S. HRG. 101-460

CONSUMER PRODUCTS SAFE TESTING ACT

HEARING

BEFORE THE

SUBCOMMITTEE ON THE CONSUMER

OF THE

COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION UNITED STATES SENATE

ONE HUNDRED FIRST CONGRESS

FIRST SESSION

ON

S. 891

TO PROVIDE FOR THE MODERNIZATION OF TESTING OF CONSUMER PRODUCTS WHICH CONTAIN HAZARDOUS OR TOXIC SUBSTANCES

NOVEMBER 8, 1989

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CONSUMER PRODUCTS SAFE TESTING ACT

WEDNESDAY, NOVEMBER 8, 1989

U.S. SENATE,
COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION,
SUBCOMMITTEE ON THE CONSUMER,
Washington, D.C.

The subcommittee met, pursuant to notice, at 9:07 a.m., in room SR-366, Russell Senate Office Building, Hon. Richard H. Bryan [chairman of the subcommittee] presiding.

Staff members assigned to this hearing: Linda Lance, staff counsel; and Sherman Joyce, minority staff counsel.

OPENING STATEMENT BY SENATOR BRYAN

Senator BRYAN. Good morning. Let me take this occasion to welcome everyone to this hearing of the Consumer Subcommittee on S. 891, the Consumer Products Safe Testing Act.

As you know, this legislation was introduced by my senior colleague, Senator Harry Reid from Nevada, who joins us this morning, and companion legislation has been introduced by Representative Boxer in the House, who also joins us this morning.

Today we will obtain information on the purposes and effects of this proposal. As I understand it, this legislation is intended to minimize the use by Federal agencies of data from tests involving animals. Toward this end, the bill would prohibit use of results of a test known as LD50 by Federal agencies regulating products.

In addition, the bill would establish a new requirement for all agencies involved with premarket evaluation of the toxicity of a product. Before any animal toxicity test results could be used, the agencies would need to determine that all non-animal tests have less validity than the animal tests. Such a determination would be published in the Federal Register.

I am sure that we all share a desire to ensure that animals are treated in the most humane and ethical manner possible. There is, however, a divergence of views about the extent to which animal toxicity testing is necessary or appropriate, and this morning we will hear those divergent views.

We have an interesting and expert group of witnesses with us. Two Federal agencies, HHS and EPA, are represented by distinguished agency officials, and we look forward to hearing from them about the impact of this bill, if any, on their work.

Our second panel includes groups outside the government who have an interest in this issue. The Humane Society, the Doris Day Animal League and the Physicians Committee for Responsible Medicine all are supportive of this legislation and can provide important information to this subcommittee on the humane treatment of animals and the extent to which they believe animal testing can be reduced.

The National Association for Biomedical Research also is represented. This group will provide the views of members of the academic community and industry, and the impact of this bill, if any, on the work that they perform.

This is an issue that is important, but like many issues that confront us in the Congress, not without controversy.

We look forward to the testimony of these witnesses this morning. I am pleased this morning to acknowledge the presence of Senator Harry Reid and Congresswoman Barbara Boxer. And I am told that because Ms. Boxer has an important matter before the House, that by agreement she is to go first. We welcome you to the committee, Ms. Boxer, and will be glad to hear from you.

[The bill follows:]

101ST CONGRESS
1ST SESSION

S. 891

To provide for the modernization of testing of consumer products which contain hazardous or toxic substances.

IN THE SENATE OF THE UNITED STATES

MAY 2 (legislative day, JANUARY 3), 1989

Mr. REID introduced the following bill; which was read twice and referred to the Committee on Commerce, Science, and Transportation

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A BILL

To provide for the modernization of testing of consumer products which contain hazardous or toxic substances.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Consumer Products Safe Testing Act".

SEC. 2. FINDINGS AND POLICY.

(a) FINDINGS.—The Congress finds that—

(1) the LD50 test is an acute toxicity test on animals which has been shown to be inaccurate, misleading, and unnecessary in product testing;

(2) other tests have been developed which are less costly, more humane, and more accurate;

(3) nonanimal alternatives have been developed for other acute toxicity tests using animals;

(4) the Federal Government has encouraged the use of the LD50 test and other animal acute toxicity tests through regulations which mandate their use, encourage their use, or do not prescribe other less costly, more accurate and humane alternatives;

(5) private industry is reluctant to use other tests without encouragement from the Federal Government; and

(6) private industry and the consumer will benefit from the promotion of alternative methods of testing when these alternatives are more accurate and humane than animal tests.

(b) POLICY.—Federal departments and agencies shall encourage the development and use of product testing procedures which accurately reflect human reactions to products, including consumer products and products containing hazardous or toxic substances, but which do not rely upon animal models.

SEC. 3. FEDERAL ACTION.

(a) PROHIBITION OF USING LD50 TEST FOR PRODUCT SAFETY, LABELING, AND TRANSPORTATION REQUIRE-

MENTS.—Effective 1 year after the date of enactment of this Act, Federal department or agency heads may not consider LD50 test results when determining product safety, labeling, or transportation requirements for the purposes of Federal regulation.

(b) REGULATIONS CONCERNING TESTS OTHER THAN ANIMAL TOXICITY TESTS.—(1) Not later than 1 year after the date of enactment of this Act, each Federal department or agency head shall—

(A) review and evaluate any regulation, guideline, or recommendation issued by that department or agency which requires or recommends the use of an animal toxicity test for the purpose of pre-market evaluation of the relative acute toxicity of a product; and

(B) promulgate regulations which specify that nonanimal toxicity tests be used instead of animal toxicity tests, unless that Federal department or agency head determines that in certain limited cases the nonanimal toxicity test has less validity than the animal toxicity test.

(2) If a determination is made that a specific nonanimal toxicity test is less valid than an animal toxicity test, the appropriate Federal department or agency head shall publish in the Federal Register an explanation of all options considered and the justification for continuing the animal toxicity

test, which shall be subject to public comment before a final regulation is promulgated.

(c) PERIODIC REVIEW OF ANIMAL TOXICITY TESTING REGULATIONS.—At least every 2 years (beginning 3 years after the date of enactment of this Act), each Federal department or agency head, after considering the most recent technological advances available, shall determine whether continued use of any animal toxicity test is justified. If a Federal department or agency head determines that such a use is justified, then that Federal department or agency head shall publish in the Federal Register an explanation and justification of such continued use, which shall be subject to public comment.

SEC. 4. DEFINITIONS.

For purposes of this Act—

(1) ANIMAL.—The term "animal" means any vertebrate.

(2) ANIMAL TOXICITY TEST.—The term "animal toxicity test" means an animal model acute toxicity test including (but not limited to) the Draize eye or skin irritancy test, approximate lethal dose test and the limit test.

(3) FEDERAL DEPARTMENT OR AGENCY HEAD.—The term "Federal department or agency head" means the head of a Federal department or agency who—

(A) has authority to promulgate regulations, guidelines, and recommendations with respect to procedures to be used in the testing of products, including consumer products, veterinary products, and products containing hazardous or toxic substances; or

(B) licenses or approves products, labeling requirements for products, or the transportation of products based on the results of these tests.

(4) NONANIMAL TOXICITY TEST.—The term "nonanimal toxicity test" means a nonanimal model acute toxicity test including (but not limited to) cell culture, computer modeling, protein alteration, and chorioallantoic membrane techniques.

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STATEMENT OF HON. BARBARA BOXER, U.S. REPRESENTATIVE FROM CALIFORNIA

Mrs. BOXER. Thank you so much, Mr. Chairman. I would ask that my full testimony be submitted for the record, and I will read from it.

Senator BRYAN. That will be the order.

Mrs. BOXER. Thank you, and I thank Senator Reid, my partner in this legislation, for permitting me to go first so I can get over to the caucus on the House side.

I do thank you for this opportunity to testify before you in behalf of S. 891, the Consumer Products Safe Testing Act.

The broad support for this legislation is really difficult to overstate because thousands of letters have been mailed by individuals and groups across this country in support of the legislation. The House version of the Consumer Products Safe Testing Act currently has 103 cosponsors.

Our testing act has two parts. First it will ban any consideration of LD50 test results by government agencies, respectively stopping the use of this outdated, irrelevant and cruel test. LD50 test results vary widely due to factors such as the animal's sex or diet. The test also varies from species to species making it unreliable in relation to humans.

Although use of this test has declined in recent years, it continues to be performed due to ambiguous Federal toxicity testing requirements which explicitly or implicitly encourage use of the test simply by not renouncing it.

The second part of our bill requires that Federal agencies simply publish justification of any animal testing requirement in light of available non-animal alternatives so that we can know, if it is necessary, to use animals in this type of testing. The publishing requirement is simple and straightforward.

Mr. Chairman, I am confident that everyone in this room is in agreement on two principles: first, that the protection of human health is paramount. Americans now more than ever, are looking to their government for protection from the toxic perils of modern life. We all seek to ensure that the methods used to protect us are the most advanced and that the products we buy certainly will not harm us.

And secondly, I believe we agree that the pursuit of such a guarantee of safety is conducted in the most humane manner possible with respect to animal life. In other words, there is no point in using a cruel and inhumane test when, in fact, alternatives do exist to give us the information we need.

So, it is with these two principles in mind that Senator Reid and I authored the Consumer Products Safe Testing Act.

The classical LD50 toxicity test is a perfect example of a test which violates those two criteria: one, the best method of protection for human health, because it is not; and, two, humaneness, which it is not humane.

In 1982 the Pharmaceutical Manufacturers Association declared that use of the classical LD50 test lacks justification. That's a quote directly from them. Large numbers of animals are killed in the performance of an LD50, and better methods than the LD50 exist for ensuring human safety.

Now, what about our government organizations? Federal agencies such as FDA, EPA and the Consumer Product Safety Commission have made public pronouncements, Mr. Chairman, that the LD50 test is, indeed, not necessary for the testing of consumer products and that the use of animals should be minimized whenever possible.

However, despite the conviction of their pronouncements and the responsibility of their own practices, the actual language of the requirements, protocols or recommendations which the agencies impose on industry do not advance this same thinking. Companies still have the option—and some continue to use it—of submitting LD50 test results. So, we must go one step further and just flat out not accept those test results, discrediting the routine use of the LD50 for the ostensible purpose of protecting human health once and for all.

But, Mr. Chairman, I submit it is not enough to just get rid of the classical LD50. We must ensure that we have in place a regulatory mechanism which clearly demonstrates to industry that the government will consider non-animal alternatives for testing products and that will ensure that data from such tests will be accepted if the tests prove the equal of animal methods.

Many reputable research centers such as Johns Hopkins University have developed accurate and inexpensive non-animal alternatives such as the Ames test. However, without Federal direction, the move to use these new non-animal alternatives has been extremely slow at the expense of human safety, animal welfare and many thousands of dollars.

Now, there is a success story in all of this. Even in the absence of a clear direction, cosmetic companies such as Avon and Revlon have recently announced that they will no longer be using animals in product research and will be using only non-animal alternatives. This is exciting news, and these companies are to be commended. However, these are only two companies out of thousands and it is clearly time for the Congress to ensure that our Federal regulatory requirements are flexible and that Federal agencies will willingly employ results from legitimate non-animal testing techniques.

Recently six states have taken the issue of animal welfare into their own hands. Due to the confusing and mixed signals from our government, they have introduced legislation making performance of the LD50 and Draize tests a crime through their own state anti-cruelty statutes. And the jury is out as to whether these will pass. But, Mr. Chairman, this is an area where we should really be the leader, not the follower.

I would like to add that claims that this legislation will force all animal testing to a grinding halt are patently misleading and irresponsible. This bill is directed specifically at toxicity testing of consumer products and in no terms involves biomedical research. Additionally, while this bill bans use of the classical LD50 test in the first part, animal toxicity tests may continue to be required and the results accepted provided that they are justified.

In closing, Mr. Chairman, I truly respect and support the needs of science and so does my colleague right here with me. But we must not continue an inhumane practice when acceptable alternatives exist. I have always believed that an important measure of our society is the manner in which it treats all living things. Senator Reid's bill reflects this thinking. I am very proud to be the co-author in the House. I am proud that I came into Congress with the good Senator here, and I'm delighted to be working with him on this bill. And I hope you will see it pass into law.

Thank you, Mr. Chairman.

Senator BRYAN. Ms. Boxer, we thank you very much for your testimony this morning and understand that you need to return to the caucus.

Now we will hear from the senior Senator from Nevada, the principal sponsor, Mr. Reid.

STATEMENT OF HON. HARRY REID, U.S. SENATOR FROM NEVADA

Senator REID. Thank you, Mr. Chairman, Senator Danforth.

Why do we need this legislation? The answer is simple. Because of two outdated, unreliable and needlessly cruel lab experiments used for product research, the Draize Eye Irritancy Test and the Lethal Dose 50 Test known as LD50.

In the Draize Test, high concentrations of suspected irritants are squirted into the eyes of rabbits. The rabbits endure excruciating pain. The irritants squirted into the open eyes of these rabbits are pesticides, cosmetics, even septic tank cleaners. The drops are applied until the rabbits' eyes are painfully swollen and they cry like babies. How else could we expect these animals to respond to an experiment that is commonly called the "Rabbit Blinding Test?"

At the end of the Draize Test, the rabbits are killed. By that time, killing these defenseless animals is almost an act ot mercy.

The other experiment is the LD50 Test. This test is easy to say—LD50—but it's horrrible and gruesome to consider.

In the LD50, rabbits and other laboratory animals are force-fed poisons and other chemical substances. Window cleaners, bleach, ammonia, paint removers, car antifreeze, and oven cleaners are forced down the throats of lab animals until 50 percent of them die. That's the LD, lethal dose, 50.

It's one of the most widely used methods for testing toxicity in commercial products. The Consumer Products Safe Testing Act would ban Federal agencies from accepting LD50 tests.

But the LD50 test is not just inhumane, it is scientifically suspect and unreliable. According to an Office of Technology Assessment report on animal testing alternatives, the LD50 test has poor reproducibility. In other words, the results cannot be duplicated or confirmed in another lab, one of the foundations of sound, reliable scientific research.

The Office of Technology Assessment also concluded: "The results are difficult to extrapolate to humans because there are so many mechanisms by which death could occur." We cannot even be sure what the LD50 test means to the people who use and buy the products being tested.

In 1984, the Chairman of the Medical Research Modernization Committee called the LD50 test an anachronism. Five years later, we are still using this outdated, behind-the-times test because the written regulations have not changed. Industry believes that existing guidelines make animal testing necessary for market approval and protection in liability suits. As long as the Federal Government refuses to change the rules, companies will fail to use or create more effective tests.

The legislation of Congresswoman Boxer and myself breaks this log jam.

The Consumer Products Safe Testing Act will encourage innovation and accuracy in product testing. The bill will enable companies to find more effective and more humane testing methods.

Critics of the bill will claim that valid alternatives do not exist.

But Draize test alternatives have already been developed by the private sector. As Congresswoman Boxer indicated, Avon Corporation discontinued the Draize test in February, and are now using Eytex, a

non-animal alternative test that the company validated for its products as part of its product safety evaluation program. In fact, Avon announced in June that the company has permanently stopped using animals in the safety testing of its products. Instead, Avon utilizes alternative tests, clinical tests on people, and a massive computerized data base of ingredients and products that have been previously tested for safety.

Other companies, including Amway, Mary Kay, Revlon, Noxell and Crabtree and Evelyn, have either placed a moratorium on or have stopped altogether using laboratory animals to verify the safety of their products.

State legislatures, as previously testified, are also looking to us for a resolution of the questions surrounding the use of animals in acute toxicity testing.

In a letter to Congressman Henry Waxman, California Assemblyman Jack O'Connell wrote: "The issue of the use of animals in acute toxicity tests was recently brought before the California Assembly. This specific bill sought to criminalize the use of the Draize or LD50 skin irritancy test for the purpose of testing consumer or household products. This legislation arose out of frustration with the lack of initiative on the part of industry to change from animal to in vitro acute toxicity testing where possible without sacrificing human health and safety. As recently exemplified by Avon's initiatives, industry is capable of significant changes in this area.

"The bill failed in large part because of confusion over the Federal Government's role in determining the safety of cosmetics and household products and the government's continued support for the Draize test despite a lack of initiative to validate new technologies."

The Consumer Products Safe Testing Act calls upon Federal agencies to review these regulations regarding the Draize and LD50 tests and if non-animal alternatives exist, to substitute those alternatives. It is not fair to the consumer to continue using such tests, especially if viable alternatives exist.

Without Federal guidance to the contrary, companies conducting the Draize and LD50 tests will stick to the tried and true, but the tests have proven to be less than true. The tests are certainly cruel and certainly unreliable. When it comes to product safety, we cannot afford these half-truths.

We are not talking about a fine line. If the Draize test and the LD50 test were more reliable and less cruel, the outcry for change might not be so loud. But these two experiments fail miserably where it counts the most, on humanitarian and scientific grounds.

In the name of product development, consumer safety and scientific integrity, I urge this committee to take action and to pass this long overdue legislation.

Thank you, Mr. Chairman.

Senator BRYAN. Senator Reid, we thank you very much for your testimony, I know that you have a previous commitment, so, if you need to excuse yourself, we fully understand.

Senator REID. Thank you very much.

Senator BRYAN. The record should reflect that Senator Danforth, who is the ranking member of the full committee, joined us earlier but himself had to go to another hearing.

And I am pleased to have the ranking member of the subcommittee, my colleague and good friend, Senator Slade Gorton, who joins us this morning. Senator Gorton, I will yield to you.

OPENING STATEMENT BY SENATOR GORTON

Senator GORTON. Thank you, Mr. Chairman. You have called this hearing on what is obviously an important issue. I was delighted to hear from Senator Reid on the subject. It is obvious that it is important to ensure that consumer products are safe and that we have testing procedures for those products which are accurate.

Experts disagree about the usefulness of the tests which may be covered by this bill, though perhaps not so much on the one which is central to the bill. Some believe all of these tests to be inaccurate and inhumane as well. Others, I presume will testify that there are no alternatives to some forms of animal testing.

As a consequence, I believe that this is an important hearing and we will hear from all sides, probably multiple sides, to a complex question and then look very carefully at both the direction of the bill and its specific requirements as we decide whether or not to move forward.

Senator BRYAN. Thank you very much, Senator Gorton.

We do have a distinguished panel to help us guide us through the various points of view that are represented by this bill. The first panel this morning will consist of Dr. James O. Mason, who is the Assistant Secretary for Health and Acting Surgeon General, Department of Health and Human Services, and Mr. Victor Kimm, the Deputy Assistant Administrator for Pesticides and Toxic Substances, from the Environmental Protection Agency. I note that we have a vacant chair. Perhaps Mr. Kimm is not here yet this morning.

Dr. Mason, we are delighted to have you with us this morning. We will hear from you.

STATEMENT OF JAMES O. MASON, M.D., ASSISTANT SECRETARY FOR HEALTH AND ACTING SURGEON GENERAL, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. MASON. Mr. Chairman, Senator Gorton, it is a pleasure to have this opportunity to appear before you today, and it is critical for the subcommittee and other Members of Congress to fully understand the grave consequences that this bill would have for the Nation's health.

Enactment into law of Senate Bill 891 would have devastating repercussions for the Nation's health. The whole purpose of medical research is to improve the quality of human life through the development of new treatments and preventions that are, in effect, new products. Testing and research are inextricably linked to that process. Biomedical

research and drug development programs would be severely impeded by restrictions on the choice of scientific methods and the administrative burden of justifying the use of animals for each type of toxicity testing.

The bill's purpose is to provide for the modernization of testing of consumer products which contain hazardous or toxic substances. In point of fact, it makes state of the art animal studies the exception and elevates non-animal methods to the norm.

The results of this bill would be to reduce dramatically our ability to determine the safety of pharmaceutical and other consumer products. The presumption that non-animal models for toxicity tests can alone provide adequate information for protection of the public health and safety is simply not true. The Ames mutagenicity assay is a good adjunct to animals when used for identifying carcinogens. However, it completely misses many non-genotoxic carcinogens such as benzene, diethylstilbestrol, pentachlorophenol and others.

Some have mistakenly thought that FDA requires the use of the LD50 test. In 1985, recognizing the emergency of newer and better methods for toxicological testing, FDA revoked the regulatory requirement for the test. FDA supports efforts to eliminate the continued use of the classical LD50 test and to reduce the numbers of animals used in acute toxicity testing, but without jeopardizing the information necessary to determine the human safety of products. However, it should be recognized that in some cases other forms of the LD50 test would be necessary.

While the FDA is actively considering alternatives to the rabbit eye irritation test, it is more likely that these efforts will result in reduction or refinement as opposed to the replacement of the Draize irritation eye test.

Were S. 891 to become law, research and testing on the causes, treatment and prevention of cancer would be crippled. The delays resulting from the requirements imposed by the bill would severely retard efforts to develop and improve therapies and vaccines for human infections such as AIDS, hepatitis B, influenza, herpes and gonorrhea. The delays would also devastate toxicity testing of new drugs to treat both acute and chronic pain.

Furthermore, at a time when we are confronted by a national crisis in drug abuse, there would be unacceptable delays in developing new medications for use in the war against heroin and cocaine addiction. Before human trials can be conducted, it is absolutely essential that medications being studied as treatment agents for cocaine addiction be administered to animals to ensure the absence of lethal interactions.

Our Nation's population today is healthier than it has ever been. In large part this is due to the ethical, humane use of laboratory animals in testing drugs and other consumer products. I am convinced that the role of laboratory animals in testing and in biomedical research is necessary if we are to continue the pace of scientific progress and safeguard the public health. Given what I know about the complexity of living systems, I do not foresee a day when alternatives will replace whole animal models either in toxicological testing or biomedical research.

The Federal scientific community must continue to conduct and support the research needed to protect and improve human health as it has been charged by Congress. At the same time, however, it is also our responsibility to protect with the greatest care and compassion the experimental animals that have made our progress in improving the health of this Nation's citizens possible.

We have many, many regulations on the books, some given to us by Congress, and they are wise and judicious. But to have more regulations, as implied by this bill, would have dire consequences to the progress of science in protecting human health.

This concludes my prepared remarks. I hope that I can submit my entire testimony for the record. I would be pleased to answer any questions that you might have.

[The statement follows:]

STATEMENT OF JAMES O. MASON, M.D., ASSISTANT SECRETARY FOR HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Chairman and Members of the Committee:

I am Dr. James O. Mason, Assistant Secretary for Health and I appreciate this opportunity to comment on S. 891, the Consumer Products Safe Testing Act. I believe it is critical for the Subcommittee and the other members of Congress to fully understand the grave consequences that this bill would have for the Nation's health.

At the outset let me clearly state my belief that laboratory animals must be treated humanely. It is also important to make it clear that laboratory animals will continue to play an essential role in research and in testing products. The citizens of this Nation and people around the world deserve the benefits that these endeavors have brought and continue to bring in terms of treating, and preventing disease and disability.

The use of laboratory animals in carrying out research and in ensuring the safety of industrial chemicals, pesticides, pharmaceutical and other consumer products is critical. Toxicity data on humans are invaluable in conducting risk assessments, but such data are fortunately usually not available except as the result of occupational or accidental exposure. Thus animal model systems must be used if we are to protect health and prevent disease.

At the same time, I wish to emphasize that scientists using laboratory animals have a clear responsibility to treat these animals with the greatest care and compassion. Federal regulations and guidelines (including those of the Public Health Service), State laws, and standards developed by professional scientific societies, establish principles and procedures to ensure the humane care of these animals which are so indispensable to progress in protecting human health. The Public Health Service (PHS) has exercised great leadership in this area by continuously revising its Guide for the Care and Use of Laboratory Animals first published in 1963 and in implementing its Policy on the Humane Care and Use of Laboratory Animals at PHS intramural laboratories and at the Nation's universities, medical centers, contract laboratories, and other research institutions. Vigorous regulatory oversight helps to ensure that PHS regulations and guidelines are followed, and in the rare cases where violations or abuse are found, funds can be suspended.

The highest ethical standards and humane considerations are given to the animals used in the laboratory. We must continue to provide the best possible care and housing, using state-of-the-art technology. Animal pain must be avoided or mitigated to the fullest extent possible. The process by which we develop animal care and use guidelines and the manner in which we implement them

should continue to involve the public.

Research and Medical Advances

Before I describe the Administration's specific objections to this bill, I would like to remind the Subcommittee how dramatically our ability to prevent and treat human disease has improved. Much of this progress is the direct result of the use of laboratory animals.

During the early history of drug development, animal testing was seldom used and often the first signs of toxic side effects from a new therapy were those observed in humans. Early cures for tapeworms caused blindness. Adverse human reactions followed the introduction of quinine in the treatment of malaria, and the use of mercuric chloride for edema, which is the abnormal accumulation of body fluids. At the turn of the century, the Nobel Laureate Paul Ehrlich synthesized hundreds of compounds in his laboratory searching for a cure for syphilis. When a drug's administration proved fatal to the human patient, or if blindness or neurological complications occurred, he moved on to other compounds. This was how the first arsenicals used in the treatment of syphilis were developed. These are powerful examples of the very great need for animal toxicology testing.

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Today, an ill patient need not fear that he or she will suffer some unknown toxic side effect from a new drug, because laboratory animals are used as scientifically valid surrogates for humans in testing new pharmaceuticals. The biological processes controlling life at the molecular, cellular, tissue and organ level hold parallels from one mammalian species to another. The closer the test animal is to a human physiologically, or the greater the number of animal species in which the toxic effect is detected, the more likely it will occur in humans as well. Mice and rats constitute the species most commonly used in testing.

There are striking examples where animal studies have made a difference, or could have made a difference, for human health. This point was recently made by Dr. Irving Selikoff at a National Institutes of Health presentation for Congressional members and their staffs. He described the legacy of death and debilitating disease for thousands of workers and their families following asbestos exposure -- effects that could have been avoided had the animal models available since the 1930s and 1940s for studying asbestos been used.

At this same meeting, a young woman whose mother had taken DES (diethylstilbestrol) to prevent miscarriage told of her own very serious gynecological problems that we know today are a side effect of this drug. Her story is shared by other women who have

been exposed to DES and are at risk for vaginal cancer and reproductive problems. Men whose mothers took DES are also experiencing reproductive problems. Animal studies were critical in providing the link between DES use and genital tract cancer in women and alerting physicians to potential problems in males exposed to DES in their mother's womb.

Through chemical toxicology studies we have learned about cancer and other toxic consequences of exposure to other pharmaceuticals, certain pesticides, industrial chemicals and consumer products. Included in the appendix of my statement are several examples of such findings.

On the treatment side, tremendous advances have been made in cancer chemotherapy and other forms of drug development that would not have been possible without laboratory animal research. For example:

- All anti-cancer drugs available today are the direct result of research using laboratory animals. The principles of combination chemotherapy, which is one of the keys to curing acute lymphocytic leukemia in children, were established by laboratory studies using the LD50 test to determine whether the dose-response and toxicity curves of the treatment compounds were different or similar.

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- The severe birth defects associated with the use of Accutane, that in the past received so much media attention, were first found in laboratory animals. Animal studies not only predicted the malformations, but also allowed pinpointing of the critical exposure time during fetal development, permitting more accurate recommendations and a warning label on the prescription package insert as to when treatment should be avoided.

- Before the introduction of lithium, patients with manic depressive illness typically spent one-fourth of their lives hospitalized, and one in four patients with the illness committed suicide. Today 80 percent of these patients are never hospitalized, and patients maintained on lithium are no more at risk for suicide that any individual within the population at large. The medication, moreover, is estimated to have saved some $12 billion in medical care costs over the 20 years it has been approved for use in this country. Lithium is a product of research using laboratory animals.

Other examples could be readily cited and some of these are available in the appendix as well.

Use of Animals in Product Testing

Under the Federal Food, Drug, and Cosmetic Act (the Act), the

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Food and Drug Administration (FDA), an agency of the Public Health Service (PHS), is required to evaluate safety data submitted in support of applications for research or marketing permits for products regulated by the Agency including new drugs, biological products, new animal drugs, food additives, color additives, and certain medical devices intended for human use. Because it is unreasonable to expose people to products in which the risk of harm, injury, or illness is unknown, initial safety studies are conducted on animals. The position of the PHS is that the use of animal tests by industry to establish the safety of regulated products is necessary to minimize the risks from such products to humans.

Safety testing has evolved over several decades. Some useful tests have been modified and retained; others have become recognized as being inappropriate or unnecessary. An example of the latter category is the classical LD50 test. The classical LD50 test yields a statistically exact value, for the dose at which one-half of the test animals (usually rodents) can be expected to die from exposure to the test substance.

Some have mistakenly thought that FDA requires use of this test. Not so. The classical LD50 test, as opposed to other forms of the LD50 test, became generally recognized as unnecessarily precise, and, in 1985, recognizing the emergence of newer and

better methods of toxicology testing FDA revoked the regulatory requirement for the test. FDA supports efforts to eliminate the continued use of the classical LD50 test and to reduce the numbers of animals used in acute toxicity testing without jeopardizing the information necessary to determine the human safety of products. However, it should be recognized that in some cases other forms of the LD50 test are or would be necessary.

In addition, as part of its overall effort to reduce or avoid unnecessary testing methods, FDA has been carefully evaluating the use of the Draize eye irritant test which utilizes test rabbits. The Draize test is still the most reliable method for determining the potential harmfulness, or safety, of a product instilled in the eye, such as ophthalmic drugs and devices and some cosmetic products. While the FDA is actively considering alternatives to the rabbit eye irritation test, it is more likely that these efforts will result in reduction or refinement as opposed to the replacement of the Draize irritation eye test. Although most require research for validation, some *in vitro* studies are useful as screening tools to indicate relative toxicity or safety of a substance coming into contact with the eye. The Agency has provided industry with guidance relating to the use of *in vitro* methods to support the safety of products subject to eye irritancy testing.

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Although the Act does not require that cosmetic manufacturers or marketers test their products for safety, the FDA strongly urges cosmetic manufacturers to conduct toxicological and other appropriate tests to substantiate the safety of their products. Depending on how the cosmetic is used, such as applying to the area of the eye or to the skin, the following toxicological tests may be done: acute oral test for potential accidental poisoning; six hour inhalation test to determine toxicity if breathed in; eye and dermal irritation tests to determine toxicity to the eye and skin, respectively; skin sensitization test to determine the product's allergic potential; and a phototoxicity test to determine the potential of sunlight interacting with the product and thereby causing toxicity. The FDA cannot condone the use of any potentially harmful substance in humans without first conducting preliminary testing in animals to provide reasonable assurances that it is not injurious to humans. Since certain tests should never be carried out in human beings and since at the present time there are no adequate alternatives, whole animal testing remains essential.

Research Methods

It is misleading to use the phrase "alternatives to animals." Instead, most scientists advocate the use of phrases such as "adjuncts to animals." This is because studies involving non-

animal models of human processes complement those involving animal models, but rarely replacement them. Research and testing models commonly referred to as "alternatives" include other living systems such as microorganisms, invertebrates, in vitro cultures of cells, tissues and organs, and non-living models such as mathematical, computer and physical simulations that mimic biological functions. While many of these systems have been shown by scientific means to be valid models for human processes in certain circumstances, they cannot substitute for the biological data gained from the whole animal. Whole animals are essential in research and testing because they best reflect the dynamic interactions between the various cells, tissues and organs comprising the human body.

We must be realistic in accepting the limitations of non-animal methods. Validated non-mammalian systems can and do complement whole animal studies, providing some very precise and useful information. However, these non-mammalian systems cannot substitute for the biological data gained from using laboratory animals.

For many chemicals, the carcinogenic and toxic effects they produce in animals or humans are simply not revealed in in vitro testing, for example. The drug cyclosporin, an immunosuppressive drug widely used in organ transplantation operations, is a case

in point. *In vitro* tests of this antifungal agent did not indicate its immunosuppressive capabilities. This drug was only shown to be immunosuppressive in whole animal studies. Because of the immunosuppressive effects of cyclosporin, life saving kidney, liver, heart and pancreas transplantation operations have been made possible.

Implications of S.891

Enactment into law of S.891 would have devastating repercussions for the Nation's health. Because the whole purpose of medical research is to improve the quality of human life through the development of new treatments and preventions that are in effect new products, testing and research are inextricably linked. Biomedical research and drug development programs would be severely impeded by restrictions on choice of scientific methods and the administrative burden of justifying the use of animals for each type of toxicity testing. The bill purports to "provide for the modernization of testing of consumer products which contain hazardous or toxic substances." In point of fact, it makes state-of-the-art animal studies the exception, and elevates non-animal methods to the norm.

The result of the bill would be to reduce dramatically our ability to determine the safety of pharmaceutical and other

consumer products. The presumption that non-animal models for toxicity tests can alone provide adequate information for protection of the public health and safety is simply not true. If in vitro tests alone had been used, the toxicity of many asthma agents may have been overestimated. Had that occurred, reduced dosage of the drugs may have been recommended and asthma victims would have suffered needlessly. The Ames mutagenicity assay is a good adjunct to animals when used for identifying carcinogens. However, it completely misses many non-genotoxic carcinogens such as benzene, diethylstilbestrol, pentachlorophenol, and others.

Were S. 891 to become law, research and testing on the causes, treatment and prevention of cancer would be crippled. The delays resulting from the requirements imposed by the bill would severely retard efforts to develop and improve therapies and vaccines for human infections such as AIDS, hepatitis B, influenza, herpes and gonorrhea. The delays would also devastate toxicity testing of new drugs to treat both acute and chronic pain.

Furthermore, at a time when we are confronted by a national crisis in drug abuse, there would be unacceptable delays in developing new medications for use in the war against heroin and cocaine addiction. Before human trials can be conducted, it is

absolutely essential that medications being studied as treatment agents for cocaine addiction be administered to animals to ensure the absence of lethal interactions.

These are just a few of the potentially dire consequences that could result from passage of this bill.

Conclusion

Our Nation's population is healthier than it has even been. In large part, this is due to the ethical, humane use of laboratory animals in testing drugs and other consumer products. I am convinced that the role of laboratory animals in testing and in biomedical research is necessary if we are to continue the pace of scientific progress and safeguard the public health. Given what I know about the complexity of living systems, I do not foresee a day when alternatives will replace whole animal models either in toxicology testing or biomedical research.

The Federal scientific community must continue to conduct and support the research needed to protect and improve human health as it has been charged by Congress. At the same time, however, it also is our responsibility to protect, with the greatest care and compassion, the experimental animals that have made our progress in improving the health of this Nation's citizens

possible.

This concludes my prepared remarks. I would be pleased to answer any questions you may have.

APPENDIX

Examples of the use of animals models in assessing carcinogenicity :

- The industrial chemicals bischloromethylether (BCME), vinyl chloride, and 4-aminobiphenyl are among the substances first shown to be carcinogenic in laboratory animals, and only later, unfortunately, in humans.

- Animal studies also have provided us with a reasonable degree of confidence that many chemicals are <u>not</u> likely to be carcinogenic in humans. Recent examples include: epinephrine, a treatment for asthma; mace; the food additive succinic anhydride; and the large volume industrial solvent toluene (seven billion pounds are used each year).

- Studies in animals showed that the promising pesticide 2-AAF 2-acetylaminofluorene) is a potent carcinogen in several species. This information made a big difference -- 2AAF was not developed for commercial use and, thus, there was no human exposure.

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Additional examples of the use of laboratory animal models in drug development:

- Acute animal toxicity studies have enabled researchers to determine some of the special pharmacological properties of anti-AIDS and anti-cancer drug such as AZT, cisplatin, and methotrexate, and these studies have helped establish initial drug doses for humans. Acute animal toxicity studies are required by the FDA and on a **case-by-case basis, chronic animal toxicity studies may be required** to assure the safety of treatments for cancer and AIDS patients.

- Naltrexone is a narcotic antagonist developed for the treatment of heroin addiction that blocks the effects of opiate drugs. Animals were necessary for the toxicity studies to demonstrate evidence of safety required by FDA before it approved use of this medication in humans. A legal prohibition against the use of animals for toxicity studies could preclude attempts to develop a long-acting, time release form of naltrexone to improve treatment compliance and the development of other medications vital to the treatment of drug addiction.

- Lidocaine, a drug long accepted as a safe local anesthetic, is currently undergoing testing in rodents following reports of untoward nervous system effects in babies born to mothers who were given local injections of lidocaine for routine

dental procedures while pregnant.

- The optimal therapeutic doses of anti-epileptic drugs were realized through toxicological testing which established effective doses uncomfortably close to the toxic range in many cases. Animal data were essential in determining whether or not to go ahead with the development of new anticonvulsant.

Examples of developments using non-mammalian methods:

- Scientists at the National Institute of Dental Research received an award in 1986 from the Doerenkamp-Zbinden Foundation for development of a non-animal assay that rapidly detects the invasiveness of tumor cells. The system also may be used to study the effectiveness of some anti-cancer drugs.

- Important contributions to our knowledge of normal renal function and the health effects of foreign chemicals on the kidney have been made using aquatic species. For example, because of its unique anatomy the marine kidney in such species as the Southern flounder is being used by scientists at the National Institute of Environmental Health Sciences as a model for study of the excretion of toxic chemicals.

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o The Centers for Disease Control's National Institute of Occupational Safety and Health (NIOSH) is investigating the possible use of invertebrate organisms (fruit flies) in testing agents for their teratogenicity. The investigation is assessing the sensitivity and reliability of such testing.

Senator BRYAN. Dr. Mason, we thank you for your testimony. Your full statement will be made a part of the record of this subcommittee's proceedings.

My colleague, Senator Gorton, has to go to another hearing at this point.

But let me just ask a couple of questions. As I understand the proposed legislation, it would prohibit the use of LD50, and you are testifying, in your judgment, this is not an anachronistic test, that it is needed for continued research. That is a fundamental distinction and difference between the proponents of the legislation and your own position.

For those of us that are not technically well-versed in all of these medical or biomedical subtleties, why don't you tell us precisely what it is about LD50 that makes it necessary to be continued?

Dr. MASON. Well, I think I should make it clear that in many ways there isn't a big difference of opinion on the LD50 test.

Senator BRYAN. Why don't you narrow that focus then for us?

Dr. MASON. That is exactly why I mentioned that in 1985 the Food and Drug Administration changed regulations requiring the test. But there are modifications of the test which may be needed in a certain situation to make sure that a certain product is safe for human use, and to have regulations in law which would make it very, very difficult in those instances where a modification of the LD50 test were necessary, it would have such a stifling effect and a delaying effect and it would be a costly effect. And I think we have the provisions and existing laws and regulations relating to the care and humane use of animals that we can handle that without legislation that would have such a dire effect.

In other words, there ought to be the flexibility to use those tests that are felt by good scientific background and expertise to be necessary, and let's get rid of those that aren't. And I think that process is being handled by FDA, EPA and consumer protection organizations. We are moving, and I think we do not want to move any faster than we safely can. And we want to have the flexibility to use any test when it and only it can be used to really protect human health.

Senator BRYAN. Doctor, I do not want to put words in your mouth, but if I understood you correctly you indicated—and I want to put this under italics—that there may be—underscore the word "may"—occasions in which LD50 would be needed for research. And you used the word "may." May I conclude from that at this time there

is no particular type of research in which LD50 would be absolutely, in your judgment, necessary to do a proper job of research, but that your fear or apprehension is that there may come a time in which there is a test in which LD50 maybe necessary? Is that the thrust of it?

Dr. MASON. I think you are very close to it. What I am basically saying is the LD50 test has been supplanted by other more modern animal experimental methods for toxicological testing. There are modifications of the LD50 test that are still necessary that do not use as many animals. We do not use it as often, but there are times when for consumer product safety testing, for pharmaceutical testing, for medical device testing where you may want to use that. For example, I used it in my virological laboratory to determine end points related to vaccines and things of that nature.

I would want the ability to use it if I felt that was the only way that I could protect the health of a child, but I would not use it if I felt there were other methods that were more efficacious or that could be substituted for this. But to deny me or require that we go to a board or a panel and the time and the effort that that might require I think is just not indicated in today's scientific or commerce world.

Senator BRYAN. To play the devil's advocate for just a moment and to kind of lead into where your last response led us, with respect to non-LD50 testing, the legislation would require that you, in effect, make a representation that would appear in the Federal Register, that indeed there is no other alternative testing that is as good. I am paraphrasing. That is not the exact language.

And I take it that your objection to that procedure, which would not preclude, but would have an affirmative burden of proof which you and others who are involved in scientific research would have to meet, is the bureaucratic impact, the fact that it would slow the research and the testing and the evaluation period. Is that the effect of what you are telling us?

Dr. MASON. No. That is not quite what I am trying to communicate.

The bill would provide a bureaucratic and difficult solution to a problem.

But the bill also presupposes that there are all of these alternatives to the use of animals, and I do not agree with that. Rather than animal alternatives, I think we ought to talk about adjuncts to the use of animals. We ought to see this in the concept of a comprehensive system that includes both animal and non-animal methods for testing. And what this legislation presupposes is that there are all of those alternatives out there and that only rarely would one have to come back to the use of animals.

And I am saying from a standpoint of science that we still depend largely upon animals. We can use non-animal methodologies for a lot of screening, but the computer, if anything, has opened up new compounds, new substances, that ultimately are going to have to be tested in animals. You come back to the animals fundamentally every time. And so, the Ames test and a petri dish, the computer or other tests using non-vertebrates are adjuncts to the foundation which is still laboratory animals.

And this legislation would lead people to believe that there are all these alternatives and only rarely do we need to come back to animals. That is not correct at all. Animals are still from a scientific—I would not want to put a vaccine or a new therapy into one of my children or one of my grandchildren that had only been tested by a computer program or in a petri dish or a test tube. I do not see the day when the computer or the petri dish or the test tube can be substituted for an animal in the context of new pharmaceutical agents, new vaccines, a lot of products that you and I buy in the grocery store or the drugstore every day. And this legislation presupposes that we are there, and we are not there and we will not be there in the foreseeable future.

Senator BRYAN. I thank you for that clarification.

We have been joined by Mr. Kimm. Mr. Kimm, we would like to hear from you now.

Mr. KIMM. Thank you. Let me apologize for being a little bit late. We ran into some traffic accident congestion outside.

Senator BRYAN. That is understandable.

Mr. Kimm, if I might just interrupt for a moment. I see a note that Dr. Mason needs to leave to go on to another meeting. In light of the fact that we have already had a chance to question you, you may be excused. I would indicate, Dr. Mason, that we are going to hold the hearing record open for other members of the subcommittee who are not here today. If they have any questions, they will be submitted to you and we would ask for your response to those if there are any additional questions forthcoming.

Dr. MASON. We would be delighted to respond to any questions that you or the subcommittee might have.

Senator BRYAN. We appreciate your testimony. Thank you very much, Dr. Mason.

Mr. Kimm, I apologize for interrupting you, but I just got the note here. We will hear from you now.

STATEMENT OF VICTOR J. KIMM, DEPUTY ASSISTANT ADMINISTRATOR, OFFICE OF PESTICIDES AND TOXIC SUBSTANCES, ENVIRONMENTAL PROTECTION AGENCY

Mr. KIMM. With your permission, I would like to have the prepared remarks submitted for the record.

Senator BRYAN. That will be the order.

Mr. KIMM. I will try to briefly outline the essence of the testimony and then respond to whatever questions you may have.

I am happy to be here this morning on behalf of EPA to describe a little bit of our program activities as it relates to the issue at hand and comment on the pending legislation, S. 891.

Simply stated, the activities that I am associated with, the Office of Pesticides and Toxic Substances, are primarily concerned with licensing and approval of pesticides and chemicals. We in that regard would both require testing and produce assessments based on scientific data dealing with the chemical's mode of action, its potential toxicological effects and the levels of exposure that are likely to be encountered in the environment.

In connection with this work, we rely heavily on estimates of acute toxicity. We look at questions of acute toxicity as it relates to the use of protective clothing in handling these materials. We look at it in terms of packaging materials to try to ensure that things like pesticides that have potentially serious acute effects and are appropriate to come on the marketplace do so in child-resistant packaging materials.

We also face many of the other common problems associated with the application of pesticides which are fairly biologically active chemicals and for which a concern for acute toxicity is a serious day-to-day reality.

For our part, the best tests that are currently available for assessing acute effects, essentially acute adverse effects, are in fact the animal models. And although we would like to see more in vitro measures available to us, at this point in time from a scientific perspective I share Dr. Mason's view that although there are no tests that have been fully validated and we are very limited in our ability to make projections of acute toxic effects based on the information of the non-animal tests, if you will.

Nevertheless, we are very concerned and, as I will outline, have taken measures to try to reduce the numbers of animals involved in this type of testing and look forward to further progress in that regard.

In 1978 EPA established its basic testing requirements, the classical LD50 test, if you will. This involves a fairly large number of animals. Its purpose is to identify the concentration which results in death to half of the test animals with a specified statistical expectation.

We have moved on from that. In 1984 we moved to essentially renounce the classical LD50 testing and moved into a tiered approach to testing which begins with a structural analog analysis, a desk top analysis, if you will, which oftentimes enables us to stop there and not go on to any further testing.

Where we do go on to test, we are into a limit test using a smaller number of animals at a fairly high dose, and if there is no effect there, the test terminates. If there are effects, then we follow up with a second tier which again involves a smaller number of animals and involves looking at a variety of end points beyond just lethality, beyond death. And so, out of a test like that, we would get some better sense of the other activities, adverse impacts, that the chemical might have, again as a surrogate for human exposure.

In 1988 we proposed a further refinement in acute testing, and we are here trying to use techniques to even further refine, a smaller number of animals, a variety of activities that engage activities which would provide us with perhaps a somewhat cruder estimate of lethality, but at a much lower cost in terms of test animals and the other adverse effects that are of concern to so many people.

Similarly, we are involved in looking at alternatives to the currently available ocular toxicity testing which is the subject of serious concern. We have cosponsored a workshop in 1988 to look at this from a scientific perspective. We are currently engaged in interagency discussions with FDA and Consumer Product trying to find ways again, not neces-

sarily initially replacing the test system, but at least reducing the number of animals that are involved in the testing and improving our ability to project potential adverse human effects.

Again, the bottom line, if you will, of our current perception is that we in fact need acute testing that is scientifically reliable. We are faced with a situation which as a society we reject human testing for irreversible effects. Animals are truly our only currently available alternative. The in vitro tests, while they exist in some areas, have for the most part not been fully validated. And so, we are left with the need as a practical necessity for animal testing hopefully conducted under the most humane circumstances possible. And that is essentially the posture as a regulatory agency we find ourselves in.

Having said that, you will not be surprised that our testimony indicates that we would oppose the enactment of S. 891 at this time.

[The statement follows:]

STATEMENT OF
VICTOR J. KIMM
DEPUTY ASSISTANT ADMINISTRATOR
OFFICE OF PESTICIDES AND TOXIC SUBSTANCES
U.S. ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE
CONSUMER SUBCOMMITTEE
OF THE
COMMITTEE ON COMMERCE, SCIENCE AND TRANSPORTATION
UNITED STATES SENATE
NOVEMBER 8, 1989

Thank you Mr. Chairman and Members of the Subcommittee, for this opportunity to discuss the Environmental Protection Agency's (EPA) action to reduce usage of laboratory animals in acute toxicity tests and my views on S. 891.

I joined EPA in 1971 where I have held a number of management assignments including ten years as head of EPA's Drinking Water Program and three years as Deputy in the Office of Pesticides and Toxic Substances.

The Office of Pesticides and Toxic Substances regulates industrial chemicals and pesticides to protect human health and the environment. In performing this function we require and assess scientific data concerning the chemical mode of action, the toxic effects they may produce and the levels of exposure that are unsafe for humans.

We routinely assess possible adverse impacts on populations involved in the manufacture, processing and packaging of

chemicals, users of some of these agents, including homeowners and populations exposed to pesticide residues in food, water and air. The importance of acute toxicity data in making judgments about chemical safety can not be overstated. The results of acute toxicity testing are key to decisions on such things as the need for protective clothing, pesticide child-resistant packaging, pesticide application restrictions, and community-right-to-know requirements that were put in place after the incident of chemical poisoning in Bhopal, India.

Since acute toxicity data are a key part of our decisions on human protection, we must be confident that the toxicity data are accurate and scientifically sound. To date, the best tests for measuring acute effects are those that employ laboratory animals. Unfortunately, in vitro measure of toxicity have not progressed to the state where they are accepted by the scientific community. Since appropriate alternatives to animal testing are not available and since one cannot conduct direct testing in humans, we must use animal testing to assess acute hazards from chemicals. In a perfect world, however, one would want to design and employ new methods of acute toxicity testing that are more accurate, less costly and, hopefully, would eliminate the use of live animals.

While the need for the judicious use of animals for characterizing the acute toxicity properties of chemicals

remains, there are a number of actions that we have taken to reduce the number of animals employed in individual toxicity tests and to identify alternatives to animal tests. We continue to work to further reduce use of animal tests.

In 1978, EPA laid out its testing scheme for acute toxicity. It called for determination of the median lethal dose (LD_{50}) with a measure of precision of that estimate (95% confidence interval). In 1984, we revised our position and renounced the "classical" LD_{50} test that utilizes a large number of animals for a singular purpose, calculation of a median lethal dose. Instead, we suggested a tiered approach that results in the saving of animal lives. We pointed out that in a number of cases data on structural analogues may be used to estimate the toxicity of an unknown chemical thus obviating the use of any animals. When it was determined that testing was necessary, the second step was to use a "limit" test, where a small group of animals is given a large dose of the substance. In the absence of lethality, no further testing was considered. Only in the presence of effects in the limit test, would one proceed to the last tier. This was a three-dose, multifaceted testing scheme to document a range of acute adverse effects including behavioral and anatomical effects, reversibility of effects, and lethality. In other words, there is no need to destroy animal life solely to determine an LD_{50}. Instead, it is possible to combine traditional practices and use of limited numbers of animals to

record the general toxic properties of a chemical and to calculate the range of doses that produce toxic effects, including death.

In 1988, the Agency proposed a further revision of its acute toxicity testing scheme. We called for the replacement of the three-dose, multifaceted testing with abbreviated animal protocols (like the approximate lethal dose, moving averages, and up-and-down methods). In addition, we proposed using data from one instead of two sexes. Such revisions significantly reduce the number of animals needed for such testing. In my opinion these steps are the most socially and scientifically responsible ones that can be taken at this time.

We are also examining our current test requirements for another acute exposure endpoint -- ocular toxicity. A number of people have registered concern about the conduct of the Draize eye irritation test in animals. We co-sponsored a workshop in 1988 that included staff from other regulatory agencies, industry and the animal welfare community to discuss the status of eye testing. More recently, staff from the Consumer Product Safety Commission, Food and Drug Administration and EPA have begun meeting to discuss common approaches to ocular irritation testing with the view to modifying the current protocol so as to use fewer animals and make it less painful to animals.

The Agency's Office of Research and Development is also active in devising and helping to validate alternative toxicity methodologies. For instance, the Agency employs short-term tests of in vitro genotoxicity to help make decisions about carcinogenic or mutagenic potential of chemicals. EPA scientists have developed a screen for potentially teratogenic substances that employs many fewer animals than the traditional developmental toxicity test.

The actions I have just described clearly illustrate our concern about animal welfare and life. At the same time, we must adhere to the scientific standards expected by society and also meet our Congressional mandates to protect human health.

We have acted judiciously in the area of acute toxicity testing to reduce animal usage and have begun work on modifying the Draize eye test; however, to enact S. 891 at this time would be unwise. I am opposed to this legislation as it is written because it fails to reflect the scientific reality that appropriate in vitro alternatives to animal toxicity testing are not available. In addition, S. 891 creates an administrative burden without value added, in that protection of human health would not be realized.

This concludes my prepared statement. I would be happy to answer any questions that the Subcommittee may have.

Senator BRYAN. Mr. Kimm, we thank you for your testimony. Let me ask just a couple of questions.

The classical LD50 test. Is that still needed?

Mr. KIMM. No, and I do not think that it is widely applied, at least not on the kind of tests—I have tried to describe we have moved from the classical test to a modified test, and we are presently looking at a further refined test.

Senator BRYAN. I am just trying to narrow the areas of difference between the supporters of the legislation and those of you who oppose it. So, you would agree that classical LD50 testing is no longer necessary or appropriate?

Mr. KIMM. Yes.

Senator BRYAN. You have recited some evolving regulations in terms of handling animal testing. If we agree with the basic premise that we should use the most humane methods possible and only when necessary to advance the cause of science for mankind, what kind of additional restrictions, if you do not like this legislation, what do you think would be appropriate, if any?

In other words, how do we achieve that goal assuming that you recognize that we ought to do so? And I did not read your testimony to the contrary, although you are strong in your opposition to the legislation. What can we do? If not this legislation, what can be done or should be done either at the congressional level or by agency regulation?

Mr. KIMM. It is my judgment that the problem with the legislation is it is essentially absolute. It says get away from the tests altogether.

Senator BRYAN. No flexibility.

Mr. KIMM. And we are not ready to do that.

I think what we need to do is to continue through a variety of circumstances the development of alternative tests and perhaps more critically the valuation of some of the tests that are coming through the scientific literature and see if we can't evolve over time in the direction that this legislation is designed to achieve.

If that is our goal, then it would seem to me that rather than specific legislation, other than congressional oversight on the regulatory agencies, you might think of asking the agencies to come back with some focused research and development activities that would begin to look at the verification of these tests.

Senator BRYAN. Are you convinced in your own mind that, in fact, the agencies are moving in this general direction?

Mr. KIMM. There is little doubt in my mind—again, I have recited several iterations that our agency has been involved in and that other agencies have participated in --that there is certainly a recognition and a general agreement that this is the direction that we would like to go in. If there is a difference, I think it is over the time frame, the pace at which we can move in this direction.

I think DR. Mason's last remarks go to the point that there are a number of instances certainly in drugs and in therapeutic medicine in which the availability of the animals are viewed as absolutely critical, the same way that I have said that is true for acute testing for chemicals in the societal context.

I do not think anybody disagrees on the goal. The question is how quickly can we get there and can we ensure as we move in that direction that we maintain a scientifically credible way of continuing to derive the benefits from such test systems.

Senator BRYAN. Mr. Kimm, I want to make sure that I understood what you are saying. You were indicating that most, if not all, recognize the goal, but that there is a difference of opinion as to the pace, the speed with which we move.

Again, let me just be clear on the record. Are you saying that you believe that progress is being made, that movement in that direction is, in fact, occurring although there may be some difference of opinion within the scientific community as to how quickly we may achieve certain levels? Are you satisfied that that is generally true in the scientific community?

Mr. KIMM. Yes. Simply stated, yes. I think we are moving in that direction. I am sure there will be others here today who will debate the pace at which we are moving in that direction. As I say, I think that everybody agrees on the goal. The real trouble, the difficulty, is how quickly we can ge there.

Senator BRYAN. Mr. Kimm, is this goal, this consensus that you have described within the scientific community in terms of ultimate objective, something that has evolved rather recently? Does that represent a change of opinion or attitude from the historical perspective? Why don't you give us a little bit of a scientific community institutional perspective?

Mr. KIMM. I believe that it has—10 years ago if you sat down to talk about this question, can we replace animal testing, you would have found a great deal of resistance to that. I think if at a scientific meeting the issue was raised now, you would find people, as I say, moving off, no, you can't do it all, but moving on to the notion, well, we may always have to have it for some things, but certainly a greater recognition of the need to reduce the reliance on animal testing. I think that is a reasonable summary of where the scientific community is.

Senator BRYAN. Mr. Kimm, I understand what you are saying and I do appreciate your statements. All of that, of course, will be part of our record for the full committee to evaluate. Thank you so very much for joining us.

Mr. KIMM. Thank you.

Senator BRYAN. We will now hear from our next panel which will consist of Dr. Martin Stephens, The Humane Society of the United States; Ms. Holly Hazard, the Doris Day Animal League; Dr. Neal Barnard, the Physicians Committee for Responsible Medicine; and Dr. Alexander Sevanian, Associate Professor of Pharmacology and Toxicology, the University of Southern California Institute of Toxicology on behalf of the National Association for Biomedical Research.

I will give you a moment to settle in, and when you are ready, we would like to hear from Dr. Stephens first.

STATEMENT OF DR. MARTIN STEPHENS, THE HUMANE SOCIETY OF THE UNITED STATES

Dr. STEPHENS. Thank you, Mr. Chairman. I am Dr. Martin Stephens from The Humane Society of the United States. Thank you for this opportunity to testify in support of the bill which I believe will usher in the second generation of safety tests, namely, those that are alternatives to current animal tests.

The goal of this bill is to make testing more humane, and certainly that is a goal shared by the American public, as I am sure you have realized from your constituent mail. This bill simply addresses that concern.

I had many remarks to make on the LD50 test, but it seems that there is no opposition to eliminating the LD50 test. Both Dr. Kimm and Dr. Mason agreed that the test had seen better days. They talked about the need for continued animal testing on modifications of the LD50 test. This bill does not prohibit those modifications, which include the approximate lethal dose test, the limit test, the up and down method, and others. These still involve animals, but far fewer animals, and in some cases there is less suffering per animal. I think Dr. Mason was under the mistaken impression that this bill would not allow those modifications. This bill does allow those modifications.

I was going to read you a list of criticisms of the LD50 from eminent toxicologists. I feel that it is no longer necessary to do that.

Senator BRYAN. Let me invite you to just make that part of the record if you would like to do so, Dr. Stephens. You don't have to read it all, but if you would like to have that as part of the record, we are happy to do that.

Dr. STEPHENS. Dr. David Rall, who is the head of the National Toxicology Program of the Department of Health and Human Services, called the test "an anachronism." He went on: "I do not think the LD50 test provides much useful information about the health hazards to humans from chemicals." And this from the head of the agency that tests chemicals for components of the FDA, the NIH and the CDC.

He also stated that the national toxicology program itself does not use the LD50 test.

The international scientific journal ATLA states that "It is now widely recognized among toxicologists and regulators that the precise LD50 value is an . . . unattainable illusion."

Dr. Gerhard Zbinden of the University of Zurich called the LD50 "a ritual mass execution of animals."

And I could go on and on, Mr. Chairman.

The modifications of the LD50 still use animals. But the second provision of bill will see to it that eventually those modifications too might be phased out by scientific innovations.

And that second provision is the call for periodic regulatory review by the agencies. It does not say "no animal testing overnight." Agencies have the flexibility to make an evaluation. They are to go through a notice and comment period, but they have final say on this matter.

Federal agencies already claim to be monitoring progress in alternatives. Formalizing that process will give us, the American people, and Congress a means to know that things are in good hands. We can thereby monitor the progress of the agencies on this matter.

The second provision would also eliminate a problem that I have seen in attending various scientific meetings on this topic. There is a widespread impression that agencies are impediments rather than facilitators in this area. There is built-in inertia in agencies. I think this

bill will compel agencies to do the best they can in ushering in this new era of alternative tests.

S. 891 is a prudent bill. It does not call for any more public spending. In the long term it will save industry money because these tests, the alternative tests, tend to be cheaper and less time consuming.

The bill does not say "don't use any more animals in research." I think most of Dr. Mason's remarks were related to the general controversy over the use of animals in research and testing. The bill has nothing to do with AIDS, nothing to do with cancer, nothing to do with hepatitis B. The bill would allow agencies to still accept test results from the vast majority of animal tests.

What it does do is compel agencies to do their job in facilitating new alternatives. This is an approach that Congress has endorsed in the Improved Standards for Laboratory Animals Act and elsewhere. Congress is behind the concept of ushering in humane alternatives. This is not a radical proposal.

Dr. Mason spoke of a board or a panel that scientists would have to go to. There is no such panel created by this bill. So, I have no idea what he is talking about. Frankly, I heard very little from this morning's testimony that was related to this bill.

I see the bill as a very simple matter and we urge your support for it. Thank you very much.

[The statement follows:]

TESTIMONY OF DR. MARTIN STEPHENS
Before the Consumer Subcommittee
of the Senate Committee on Commerce, Science and Transportation
November 8, 1989

Mr. Chairman and members of the Consumer Subcommittee, I am Dr. Martin Stephens, director of the laboratory animals department of the Humane Society of the United States (HSUS), the nation's largest animal protection organization. On behalf of our more than one million constituents, we appreciate the opportunity to testify on S. 891, the Consumer Products Safe Testing Act of 1989 and the use of alternatives to animal tests for determining the safety of consumer products.

The alternatives approach is the cornerstone of the HSUS's policy on the use of animals in research and testing. The HSUS has been a leading animal protection organization in promoting alternative methods. For over a decade, we have written technical and nontechnical educational materials on the subject and lobbied on this issue at the federal and state level. In recognition of the HSUS's interest and expertise in the area of alternative methods, an HSUS representative was appointed to serve on the advisory board of the Congressional Office of Technology Assessment (OTA) to assist in the development of the OTA's landmark report on alternatives published in 1986. In 1987, The HSUS and the Massachusetts Society for the Prevention of Cruelty to Animals (MSPCA) convinced Congress to earmark $16 million of the Environmental Protection Agency's (EPA) research and development budget for the development of new alternative testing methods.

In short, the HSUS has played a key role in advancing the use of alternatives for laboratory testing.

I hold a Ph.D. in biology and have been the director of the HSUS laboratory animal division for the past three years. I am also the author of the HSUS monograph entitled Alternatives to Current Uses of Animals in Research, Safety Testing, and Education and an article entitled "Replacing Animal Experiments" to be published in a forthcoming book by MacMillan Press.

With this as background, we are here today to urge you to support S. 891 as a natural next step in assuring that fewer animals are needed to test consumer products and all citizens benefit from the scientific advancements of alternative methods to laboratory animal tests.

The primary aim of this bill is to promote the development and implementation of more humane and more accurate methods of testing consumer products.

Some amplification of what "alternatives" mean may be helpful. Refinement, reduction and replacement are the 3 Rs of the alternatives approach. First, procedures can be modified so that the animal subjects experience less pain or suffering. This is known as refinement. Second, procedures can be modified so that fewer animals are needed per test. This is known as reduction. Third, and most relevant to this discussion, animal-based

procedures can be replaced by non-animal substitutes when such substitutes are available. This is known as replacement.

For alternatives such as these to be adopted, they generally must be equal to or superior than their animal-based counterparts in scientific value, or have some other attractive feature such as being more economical or less time consuming. On today's market, we already have a number of them being made available, which I describe in the attached appendix.

THE CONSUMER PRODUCTS SAFE TESTING ACT

S. 891 fosters an increased use of alternatives in two ways. First, federal agencies could no longer consider the LD50 test results when assessing product safety, labeling, or transportation requirements. Manufacturers of consumer products would thereby be discouraged from conducting this animal test (although they would not be prohibited from doing so). Second, federal regulators would have to periodically review any policies that require or recommend animal toxicity tests and justify any continued requirements or recommendations of these tests in light of any developments in non-animal alternatives. Each of these provisions will be discussed in turn.

The LD50 Provision

No aspect of animal testing has been as frustrating as the continued use of the LD50 test, an outmoded and extremely inhumane procedure developed in the 1920s. The abbreviation "LD50" stands for "Lethal Dose 50%" -- this is the dosage of a test substance at which half the animals used in the test succumb to poisoning. The LD50 test is conducted as follows: From forty to two hundred laboratory animals are used to test a substance. The most common approach is the oral LD50 in which animals are force-fed the test substance and observed for two weeks or until death. Animals that survive the study are then killed. Other test methods include: 1) an inhalation LD50 test in which animals are forced to breathe the test substance in a vapor, fine powder, or spray; 2) a dermal LD50 test in which the test substance is applied directly to an animal's skin or; 3) an injectable LD50 test in which the test substance is injected into an animal's body. Regardless of which test methods is adopted, common signs of poisoning prior to death include bleeding from the eyes, nose, or mouth, inability to breathe, convulsions, tremors, paralysis, and coma.

In 1984, an estimated 4 to 5 million animals in the United States died as a result of this test. What has been particularly disturbing is that the LD50 test has been widely criticized by toxicologists on scientific grounds that it is not an accurate indication of the potential effect of the substance on a

person. Furthermore, modifications of the test utilizing far fewer animals are available. These tests include the Approximate Lethal Dose (ALD) test, the Up and Down test and the Limit test. In the ALD test each animal is given a dose 50% higher than the one given to the previous animal. This procedure continues until a lethal (or fatal) dose is reached. This procedure yields results that correlate well with the traditional LD50, yet it uses only 6 to 10 animals per test -- a dramatic reduction in the number of animals needed. In the Up and Down test, each animal receives a single dose, but that dose changes as the 6 or so animals are sequentially tested. The dose is lowered after signs of severe toxicity develop or is raised after an animal survives one week without such signs. The resulting information is evaluated in a commonly available computer program. This procedure yields a reasonable estimate of the LD50 value. In the Limit test, a group of 10 to 20 animals is given a single dose of a test substance. If no ill effects are seen, no further testing at higher doses is required. The accepted maximum dose for the test depends on the nature of the substance being tested. The Limit test is especially useful for relatively harmless substances which would necessitate unrealistically large doses in the LD50 test.

There are also tests available which utilize no animals at all but rely instead on such procedures as <u>in vitro</u> cell cultures to reach determinations of the impact of a substance on an animal. These other tests are in various stages of development.

Timing on your consideration of S. 891 is particularly appropriate inasmuch as the Environmental Protection Agency (EPA) has begun to express some interest in eliminating the test. In September 1988, EPA issued a revised policy on acute toxicity testing on animals, which encouraged industry to make greater use of alternatives to the LD50 such as the ALD test, the Up-and-Down test and the Limit Test. In fact, the authors of the policy report that "We plan to accept only newly generated industry data that conforms with our revised guidance unless an adequate rationale...accompanies the submission; data without a rationale may be returned to the submitter.". But EPA needs help if it is to ultimately eliminate the LD50 test as an accepted test as quickly as possible. Senator Harry Reid's bill, S. 891, would be helpful in accomplishing this.

To be sure, there are manufacturers that have eliminated or all but eliminated the LD50 test. The consensus among scientists participating in the second symposium of the Johns Hopkins University Center for the Alternatives to Animal Testing held in 1983 was that reduction alternatives could completely replace the LD50 test. In 1984, Allied Corporation abandoned the LD50 test in favor of the Up and Down test. According to a trade association survey reported in 1985, the U.S. cosmetics industry has substituted the Limit test for the LD50 test and thereby reduced animal use by 75 to 90 percent.

However, despite this effort and other encouraging developments, the LD50 is still in use. Unfortunately, exact figures on its prevalence are unknown because companies are not required to report usage patterns.

Why do some companies continue to use this test? There is no basis to the argument that existing substitutes for the LD50 test, which use far fewer animals, do not yield the precision of the full blown or classical LD50 test. In effect, the shortcomings of the classic LD50 test render the quest for precision a hopeless endeavor. According to world renowned toxicologist Gerhard Zbinden of the University of Zurich, the LD50 value depends on a host of biological and extraneous factors, including:

> ...species, strain, sex, age, and weight of the animals, abundance and composition of diet, volume and speed of administration of the test substance, vehicle, solubility, and particle size, concentration, ambient temperature, housing conditions, and even the seasons of the year.

He concludes, "This means that the LD50, even if it is determined with high precision with a large number of animals, is not a biological constant." (emphasis added)

That such precision is indeed illusory, Zbinden makes clear elsewhere in his report:

> The marked species differences in acute toxicity are well recognized, making it impossible to predict the human lethal dose from the results of animal

> experiments. With such enormous variations between species, it is clear that the knowledge of the LD50 in a mouse or a rat does not provide much support for the prognosis in a human case of acute poisoning.

The evidence suggests overwhelmingly that LD50 values are highly variable within the same species and that applying such values to other species, say from mouse to man, is crude at best. Therefore, efforts to make lethal dose values more precise by using large numbers of animals are pointless.

Companies continue to use the LD50 test in many instances because they have always used it. In short, they know that despite pronouncements from EPA and others, agencies still accept these test results. S. 891 would make it clear that companies would ultimately need to utilize other more effective and more humane tests.

S. 891 has a second provision to expedite the movement toward the better and more humane science of alternatives: it is the process of consistent regulatory review.

The Regulatory Review Provision

This bill requires federal agencies to periodically reassess the need for regulations that encourage or require animal testing with the aim of phasing in alternative testing methods. This provision does not force agencies to adopt

alternative methods, simply to review their adequacy. We hope that the agencies are already monitoring progress in alternatives. If that is the case, as agencies claim, this provision would impose a minor burden on those agencies. However, even if the agencies are already monitoring this progress, S. 891 would formalize this process and compel regulators to justify any changes or lack of changes in their regulatory scheme vis-a-vis animal testing.

The Reid bill comes at a time when the animal protection community and industry are seeking greater involvement, if not leadership, from the agencies. However, federal agencies are perceived as an impediment, not only abdicating a leadership role but also failing to specify to industry how to complete development and validation of alternative methods to the agencies' satisfaction. This inertia was also highlighted in the OTA report. The bill could end this problem.

Notwithstanding our enthusiasm for the regulatory review provision in S. 891, the HSUS recommends that this provision be amplified to encourage the phasing in of not only replacement alternatives, but also reductions and refinements in other testing on animals.

GENERAL COMMENTS

The alternatives approach provides a means of reconciling the sometimes conflicting priorities of the animal protection community and other entities conducting animal testing of products. New alternative methods can and already have been shown to yield a win-win situation with animal suffering eliminated and a laboratory goal achieved. One alternative test which already achieves this is the Eytex test. This test uses synthetic rabbit-eye proteins and is said to be more economical, convenient and reliable than the Draize test, an eye irritation test in which substances are sprayed or dropped into the eyes of live rabbits. The Eytex test has already been put in use by Avon, Noxell, and other corporations.

The key to progress lies not only in the development of new alternatives, but in their validation -- systematically testing a variety of chemicals on the alternative test to ensure that it will adequately protect public health. In the area of consumer products, the bottleneck increasingly appears to be at the validation/acceptance end, not the development end. Federal agencies need to play a more active role. If S. 891 becomes law, agency inertia will end and industry can move forward in what we hope is a growing commitment to using the better and more humane science -- the science of alternatives in laboratory testing of consumer products.

We will continue to monitor industry and urge its active role in reduction, refinement and ultimately replacement of the use of animals for product testing. We are hopeful that more companies will join Avon, Revlon and Faberge, for instance, companies that have already phased out animal testing and phased in alternative tests. But we do need to enlist Congress in this effort to ensure its timely success.

In conclusion, the HSUS urges this Subcommittee to support S. 891 so that federal agencies officially become agents of change in the worthy endeavor of making animal testing of consumer products more humane and ensuring that the better science -- the science of alternatives, is utilized for testing consumer products. The HSUS looks forward to working with this Subcommittee on turning this goal into reality.

APPENDIX TO TESTIMONY OF DR. MARTIN STEPHENS, HSUS

Newer methods of testing fall into four categories:

* **Test-tube methods** - Known as "in vitro" methods, these procedures test the effects of substances on isolated cells, tissue fragments, or organs. An advantage of these methods is that researchers can test directly on human matter. Human eye tissue, for example, is available from eye banks and eye research centers. The Clonetics Corporation (San Diego, CA) markets the Neutral Red Assay, an in vitro eye-irritation test. Neutral red is a dye that is readily absorbed by healthy, undamaged human cells; irritants impair the cell's capacity to absorb the dye. The degree of absorption impairment is a measure of irritancy potential.

* **Chemical assays** - National Testing Corporation (Palm Springs, CA) markets a chemical test kit for estimating eye irritancy. The kit contains a mixture of synthetic chemicals that recreates key chemical components of the cornea. The test chemicals, like those in the eye, turn cloudy in response to irritants. The procedure, known as the Eytex Test, uses the degree of cloudiness as a measure of irritancy.

* **Non-sentient organisms** - Single-celled organisms and other animals with limited or no capacity for suffering are nevertheless sensitive to many irritating or poisonous substances. One of the most promising alternatives to the Draize Eye-Irritancy Test involves chick embryos that have not yet developed to the point where they can feel pain, but that have an outer membrane which responds to irritants. The membrane is exposed by cutting a small window in the shell. A plastic ring placed in the membrane serves as a well for the test substance. The degree of membrane response (cloudiness, inflammation, and proliferation of blood vessels) is a measure of irritancy.

* **Computer models** - These models can help predict hazardous effects based on a substance's chemical and physical properties. The models rely on the information accumulated on already tested compounds to help predict the effects of untested compounds. Based on this principle, Health Designs, Inc. (Rochester, NY) has developed computer models that estimate LD50 values, Draize eye-irritancy scores, and other test results.

Senator BRYAN. Thank you very much, Dr. Stephens.
Ms. Hazard, we will hear from you now please.

STATEMENT OF HOLLY HAZARD, EXECUTIVE DIRECTOR, DORIS DAY ANIMAL LEAGUE

Ms. HAZARD. Thank you, Chairman Bryan.

This bill addresses two concerns with regard to acute toxicity testing. First, as has been indicated by earlier speakers, the bill addresses the continued use of the classical LD50 test. The government has issued various guidelines and policy statements that it does not require the classical LD50 test. Dr. Kimm, as we heard this morning, said that his agency renounces the use of this test.

However, reports continue to surface that this test may still be considered an appropriate methodology and that individuals within U.S. agencies continue to encourage its use. For example, in a recent article on government progress regarding the changes from animal to non-animal methodology in The Alternatives Report, the author stated that "it would not be surprising if one continued to hear stories of individuals at FDA requiring companies to submit 'classical LD50 data'."

At European Commission hearings on October 26 of this year concerning the proposed elimination of the requirements for the classical LD50 test, one of the speakers applauded the commission's decision to eliminate these requirements, but stated that "the European Commission has thrown down the gauntlet to the U.S. and Japan. It is no longer a question of science, it is now up to the politicians."

And I received this morning some information that the Japanese Ministry of Health and Welfare has also decided now to abolish the obligation for the classical LD50 test for approval of new drugs coming out of that country.

It is shocking the European officials have been given the impression that this test is necessary to satisfy U.S. regulations when these same regulators have repeatedly made public statements to the contrary.

The evidence is uncontroverted that the classical LD50 test is useless and it is cruel. This Congress has the ability to ensure that this test will never be performed with the excuse that it is sanctioned by U.S. regulatory authorities. Enactment of this legislation will send a message to Federal agencies, to U.S. businesses and to our trading partners that the classical LD50 test is dead. And in the process, it will spare many animals unconscionable pain and suffering.

The second section of this bill deals simply with modifying outdated Federal regulations. It does not deal with medical research, and it does not ban animal tests. It is not an "inflexible' section of the bill as was indicated by one of the earlier panelists, and it cannot cripple research because every change that is approved in this section of the bill must be approved by the very agencies that were represented here today.

The second section merely requires Federal agencies to look at what the possible alternatives may be to the animal tests and in those areas where they feel comfortable that those non-animal methodologies can satisfy everyone's concerns for human health, they are required to ask that industry switch to the non-animal methodologies.

The Federal agencies have paid lip service to the demand that more humane methods be implemented by issuing a number of policy statements on animal testing. The Consumer Product Safety Commission issued its animal testing policy in 1984. In it the agency declares that "neither the FHSA nor the Commission's regulations require any firm to perform animal tests."

However, this same agency stated in March of 1988 that "acute toxicity tests such as the Draize test are necessary to facilitate the appropriate labeling of hazardous products."

This agency is not alone in its double-talk on this issue. The Environmental Protection Agency has made significant modifications in its requirement for animal testing. It should be commended for this. However, this same agency stated in hearings on this same bill in the House that "appropriate alternatives to animal toxicity testing are not available at this time."

The Food and Drug Administration has stated conversely that it has no authority to require that any animal tests be conducted by industry and that it will continue to "insist' that animal tests be conducted for products under its jurisdiction.

Obviously, these statements have led to confusion by industry as to what alternatives, if any, may be accepted by government regulators.

A few corporations that have been referenced earlier today have announced recently that they are going to switch to non-animal methodology. The government's public reaction to these announcements has been silence. In meetings with the parties involved, the FDA has voiced its displeasure, but has declined to take any action to require that the animal tests be performed. This, of course, begs the question of what government insistence on animal tests may mean.

Perhaps more significant than the government's continued reliance on animal testing is its lack of initiative in even investigating what the alternative tests may be. In response to a recent FOIA request that I filed with the FDA and the CPSC, the agencies could provide no documents related to scientific evaluations of either the Draize test or the alternatives to the Draize test. In fact, the Consumer Product Safety Commission responded to my request by stating: "The Commission's Directorate for Health Sciences have informed us that the Commission has not conducted evaluations of the Draize eye test, LD-50 test, skin irritancy tests or other acute toxicity tests and non-animal tests.'

These same agencies have stated that alternatives are not available, but they cannot provide any evidence that they have even looked at what these alternatives are.

The American public has lost patience with industry and with government on this issue not because of a lack of scientific progress, but because of a lack of regulatory progress.

S. 891 merely requires the government to consider alternatives to animal tests, and it is a modest step toward resolving this emotionally charged issue.

Two years ago when this issue was being debated in the House, government and industry argued that the review required by this bill was unnecessary, that alternatives weren't available and that the government was monitoring change. If this was the case two years ago, it is certainly not true today. If agencies continue to discount alternatives because they can't be used for all testing criteria or because the standard for the measure of toxicity is the product's effect on an animal as opposed to its potential effect on humans, the advancements of science in this area will continue to be stifled and animals will continue to suffer unnecessarily.

Given the scientific evidence available that human safety concerns do not need to be discounted at the expense of more humane treatment of animals, the Doris Day Animal League urges this committee to support the passage of S. 891.

Thank you.

[The statement follows:]

Testimony of
Holly E. Hazard, Executive Director,
Doris Day Animal League

Thank you Chairman Bryan and members of the Sub-committee for this opportunity to present testimony in support of S. 891.

I am an attorney with over five years of experience working on the issue of the use of animals in product testing at the state and federal level. The Doris Day Animal League, with over 310,000 members nationwide, has focused attention on the issue of the use of animals in acute toxicity tests because, unlike many issues confronting legislative bodies, a clear solution exists to the pain inflicted upon animals in the name of product safety. We have become frustrated because, despite the increasing scientific evidence that many tests are unnecessary and that government regulations are cumbersome and outdated, the tests continue to be performed. S. 891 will bring flexibility to federal regulations and give innovative technology in this area equal footing with animal testing for the purposes of government regulation.

This Bill addresses two concerns with regard to acute toxicity testing. First, the bill addresses the continued use of the classical LD-50 test. The government has issued various guidelines and policy statements that it does not require the classical LD-

50 test. Specifically, the Consumer Product Safety Commission (CPSC), with authority over the Federal Hazardous Substances Control Act, has stated that it has a policy to discourage the classical LD-50 test.[1] The Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) have both stated that they do not require or encourage the continued use of this test.[2] Also, a consensus exists within industry that the use of the LD-50 test is unnecessary and inhumane.[3]

However, reports continue to surface that this test may still be considered an appropriate methodology and that individuals within U.S. agencies continue to encourage its use. For example, in a recent article on government progress regarding the changes from animal to non-animal methodology in "The Alternatives Report," the author stated that:

> ... it would not be surprizing [sic] if one continued to hear stories of individuals at FDA requiring companies to submit "classical LD-50 data"[4]

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[1] 49 FR 22522.

[2] "Revised Policy for Acute Toxicity Testing," United States Environmental Protection Agency, Washington, D.C. 20460, September 22, 1988, at 2.

50 FR 19675.

[3] See, for example, Testimony of Dr. Gerhard Zbinden before the Sub-committee on Health and Environment, Committee on Energy and Commerce, U.S. House of Representatives, Serial No. 100-134. Attached as Exhibit A.

[4] The Alternatives Report, Center for Animals and Public Policy, Tufts School of Veterinary Medicine, Grafton, MA, Vol. 1, Number 1, June, 1989, at 2.

Further confusing the issue of the U.S. Government's position on the classical LD-50 test are the reports that U.S. advocates of the continued use of the LD-50 test attempted to thwart the modification of the European Commission's Guidelines to stop the use of the LD-50 test. At European Commission hearings on October 26, 1989 concerning the proposed elimination of the requirements for the classical LD-50 test, one of the speakers applauded the Commission's decision to eliminate requirements for the LD-50 but stated that:

> "The European Commission has thrown down the gauntlet to the U.S. and Japan. It is no longer a question of science, it is now up to the politicians."[5]

It is shocking that European officials have been given the impression that this test is necessary to satisfy U.S. regulations, when those same regulators have repeatedly made public statements to the contrary.

The evidence is uncontroverted that the classical LD-50 test is useless and cruel. This Congress has the ability to ensure that this test will never be performed with the excuse that it is sanctioned by U.S. regulatory authorities. Enactment of this legislation will send a message to federal agencies, U.S. businesses and to our trading partners that the classical LD-50 test is dead. In the process, it will spare many animals unconscionable pain and suffering.

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[5] Ben Webb, "Death-Knell for LD-50?," Nature, October 26, 1989. Attached as Exhibit B.

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The second section of the bill will assure scientists who are interested in pursuing research in computer-modeling, chemical testing, cell culture or other non-animal testing methods that if their research yields results that are as valid as animal tests, the efforts to market a new test will not be stifled by rigid government regulations requiring old test methods. Currently, confusion reigns as to what tests are required, what tests are encouraged, what tests are necessary to protect human health and what alternatives to animal tests may be available.

The federal agencies have paid lip service to the demand that more humane methods be implemented by issuing a number of "Policy" statements on animal testing. The Consumer Product Safety Commission issued its "Animal Testing Policy" statement in 1984.[6] In it, the agency declares that:

> neither the FHSA nor the Commission's regulations require any firm to perform animal tests.

However, this same agency stated in a March 9, 1988 letter to the Honorable William Horne of the Maryland Assembly that:

> acute toxicity tests such as the Draize eye irritation test are necessary to facilitate the appropriate labelling of hazardous consumer products.[7]

This agency is not alone in its double-talk on this issue.

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[6] 49 FR 22522.

[7] Letter to Honorable William S. Horne, Chairman, Judiciary Committee, House of Delegates, Annapolis, Maryland 21401-1991, from Andrew G. Ulsamer, Ph.D., Associate Executive Director, Directorate for Health Sciences, U.S. Consumer Product Safety Commission, March 9, 1989.

The Environmental Protection Agency has made significant modifications in its requirements for animal testing. It recently revised its guidelines to allow for a "tiered" approach to testing and stated that the EPA:

> urges industry to begin submitting data obtained with alternative methods which use fewer animals on a routine basis.[8]

This same agency stated in hearings on this bill in the House that "appropriate alternatives to animal toxicity testing are not available at this time."[9]

The Food and Drug Administration (FDA) has stated conversely that it has no authority to require that animal tests be conducted by industry,[10] and that it will continue to "insist" that animal tests be conducted for products under its jurisdiction.[11]

Obviously, these statements have led to confusion by industry as to what alternatives, if any, may be acceptable to the government regulators.

A few corporations such as Avon, Revlon, Christian Dior,

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[8] Revised Policy for Acute Toxicity Testing, United States Environmental Protection Agency, Washington, D.C. 20460, September 22, 1988.

[9] Testimony of John A. Moore, Assistant Administrator, Office of Pesticides and Toxic Substances, before the Sub-committee on Health and Environment, U.S. House of Representatives, May 16, 1987, Washington, D.C.

[10] Letter to the Honorable Barbara Boxer, U.S. House of Representatives, Washington, D.C. from Hugh C. Cannon, Associate Commissioner for Legislative Affairs, Food and Drug Administration, September 22, 1988.

[11] Speech, Dr. Gerald B. Guest, Director of Veterinary Medicine, May 16, 1987, Food and Drug Administration, before the Food, Drug and Law Institute, September 7, 1989.

Redken and Amway have announced recently that they have found alternatives to animal tests to be valid and that they would no longer use animals in testing. The government's public reaction to these announcements has been silence. In meetings with the parties involved, the FDA has voiced its displeasure but has declined to take any action to require that the animal tests be performed. This, of course, begs the question of what government "insistence" on animal tests may mean.

Unfortunately, the majority of manufacturers have not been as bold as those mentioned above. Members of the Animal League have received letters from dozens of U.S. corporations including Beechum Products, Johnson Wax, Lever Brothers, Gillette and Dial Corporation explaining their continued reliance on animal models. These corporations unanimously cite government regulations as one of the reasons that they must continue to use animals in testing.

In state legislatures throughout the United States, the Cosmetics Toiletries and Fragrances Association has listed federal requirements has one of the primary reasons for its opposition to state bills to ban these tests.

Amway Corporation, one of the companies which has gone "cruelty-free", has stated that because of the requirements of the Environmental Protection Agency, it has decided against introducing a new pesticide.[12]

Perhaps more significant than the government's continued

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[12] "Amway Corp. Ends Tests of Products on Animals," Wall Street Journal, August 21, 1989, at 12A.

reliance on animal testing is its lack of initiative in even investigating what value the alternative tests may have. In response to a recent FOIA request filed by the Doris Day Animal League with the FDA and the CPSC, the agencies could provide no documents related to scientific evaluations of either the Draize test or the alternatives to the Draize test. The Consumer Product Safety Commission responded to this request by stating:

> The Commission's Directorate for Health Sciences have informed us that the Commission has not conducted evaluations of Draize eye test, LD-50 test, skin irritancy tests or other acute toxicity tests and non-animal tests ...[13]

This recalcitrance on the part of the Federal Government has stifled the development of alternatives and damaged corporations which have invested in technologically-advanced methodologies. It has led to such frustration at the state level that at least six states have considered limiting these animal tests for the products under their jurisdiction. State legislators have been forced to take up this cause because of intense and increasing public opposition to the continued use of animals in product testing and complete indifference on the part of the federal government to the concerns of the public and the plight of the animals involved.

According to a recent poll conducted by the American Medical Association, three quarters of the American public oppose the use

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[13] Letter to Ms. Holly Hazard, Executive Director, Doris Day Animal League, from Todd A. Stevenson, Freedom of Information Office, U.S. Consumer Product Safety Commission, October 24, 1989.

of animals in cosmetics testing.[14] Editorials in newspapers from Boston to Green Bay to San Antonio have called for a cessation of animal testing in this area or congratulated the firms that have quit.[15] The American public has lost patience with industry and with government on this issue due, not to a lack of scientific progress, but a lack of regulatory progress.

Senate Bill 891, which merely requires the government to consider alternatives to animal tests, is a modest step toward resolving this emotionally charged issue.

Two years ago, when this issue was being debated in the House, government and industry argued that the review required by this bill was unnecessary, that alternatives weren't available and that the government was monitoring change. If this was the case two years ago, it is certainly not true today. Alternatives are available and have, in fact, been adopted by several reputable firms. However, it is clear that progress has been stifled by the irresponsible lack of action on the part of our federal government.

If industry and scientists continue to believe that innovative testing techniques will be rejected by the agencies from which they must gain approval for marketing their products, research and testing in this area will stop. If agencies continue to discount alternatives because they can't be used for all testing criteria

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[14] Public Attitudes About the Use of Animals in Biomedical Research. Prepared for the American Medical Association, September, 1989.

[15] See Exhibit C.

or because the standard for the measure of toxicity is a product's effect on an animal as opposed to its likely effect on a human, the advancement of science in this area will continue to be stifled and animals will continue to suffer unnecessarily.

Given the scientific evidence available that human safety concerns do not need to be discounted at the expense of more humane treatment of animals, the Doris Day Animal League urges this Committee to support the passage of S. 891 which will require the government to begin a process of evaluating alternative tests as they become available and will expedite the transfer of scientific technology to implementation by regulatory agencies for the purposes of ensuring the safety of consumer products.

Senator BRYAN. Ms. Hazard, we thank you very much for your testimony.

Dr. Barnard, we will hear from you next.

STATEMENT OF NEAL D. BARNARD, M.D., PRESIDENT, PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE

Dr. BARNARD. Thank you for the opportunity to testify regarding this bill.

I think it is important to know what we are talking about when we look at this piece of legislation because as I listened to the previous panel, it was apparent to me that they were not addressing the provisions of the bill.

The bill does not ban the LD50, as I read it. Companies could use the LD50 if in their judgment it was an important test. However, it could not be the basis for regulation by a Federal agency.

And as you have heard already, the LD50 is no longer of interest to EPA or FDA and neither of the previous speakers could give any examples where the LD50 should be used. That is the common opinion of toxicologists. What this bill would allow is a removal of the use of LD50 as a basis for regulation.

That is an extraordinarily important step. It should have been taken long ago.

What is the LD50? Is it a good means for regulating chemicals?

In an LD50 test the lethal dose of a compound is determined by feeding increasing amounts to various groups of animals to determine the dose at which half of them are dead. So, you dose the animals one time and you go back each day into the laboratory to look in the cages and see which animals are dying, which are dead, and at some point you will find a dose at which about half are dead. Obviously, the other half will wish they were dead because they have been dosed with the same amount that happened to kill their cage mates.

This extraordinarily cruel and extremely crude measure of toxicity was developed in 1927, 62 years ago. There is very little else in toxicology that was state of the art in 1927 that is still embraced today. It should certainly not be the basis of regulation by any Federal agency.

It gives quite variable results. Different species have widely different LD50s. For example, acetaminophen, a common pain reliever, has an LD50 of 250 milligrams per kilogram in mice. In rats it is 1,000 milligrams per kilogram. So, using equivalent body weights, the LD50s are greatly different, and it is very hard to extrapolate the results of an LD50 to humans from rodents or from other animal species.

In the Archives of Toxicology this problem was mentioned in a review of the LD50 several years ago that said "It is thus rarely possible to extrapolate from the LD50 in animals to the lethal dose in man." That and many, many other articles have taken the LD50 to task. And, as a result, you heard the previous speaker say that it is just no longer something that is highly thought of by anyone. It is the toxicological equivalent of kicking the tires when you are purchasing a car.

Drugs need to be restricted at much lower levels of toxicity. If someone comes into the emergency room, you don't need to know what dose is certain to kill them. You need to know what dose is likely to cause sensory impairments, liver damage, and other types of organ damage. These kinds of toxicological end points are far more important than the LD50. None of these are banned by this piece of legislation.

This legislation has another excellent provision that I think is also long overdue and that is that it mandates a periodic review of animal tests versus non-animal methods. This is very timely because industry is already adopting non-animal alternatives, and it is important for government to take a role in deciding what is acceptable and what is not.

I will give you an example of this. Years ago we used to hear that there is no alternative to the Draize eye irritancy test. This test was developed in 1944 by John H. Draize, an FDA toxicologist. It is widely known to have many pitfalls, a number of inaccuracies. In large measure these result from gross differences between the rabbit eye and the human eye.

Well, a number of companies were investigating alternatives and the government did literally nothing to give them guidance in this matter. The agarose diffusion method was finally accepted by Noxell, the makers of Noxema, Cover Girl and a number of other products. They had to do this basically as a corporate decision. Had this bill already been law, they would have had guidance in this matter.

Interestingly the agarose diffusion method and related tests have been around since the early 1960s. If there had been a mandated review process, we could have replaced the Draize 25 years ago or at least we could have seen good indications of lines of research that should be pursued.

Avon has used Eytex. Noxell has used the agarose diffusion method. Colgate-Palmolive has been using the CAM test which uses a chicken egg as a replacement for the Draize. All of these methods have various strengths and weaknesses, and a number of companies are investigating using batteries of them.

'This bill would not ban any animal test, nor would it say that any of these methods is perfect or even equal to an animal test. Companies can continue to use whatever animal test they choose.'

But what it does say is that Federal regulations have to have a basis in rationality, and every two years a requirement for an animal test should be discussed and reevaluated. And the alternatives that have been considered need to be made specific. And that way we will know if Federal agencies are doing their job or simply regulating on the basis of their failure to look at these materials.

Now, there are, of course, groups that oppose any regulations of any kind on any testing, and there are other groups who would say let's end testing tomorrow. What is a middle ground? This bill is very well drawn. It is not going to ban any tests, but the most archaic of these tests should certainly not be the basis for regulation, and every other use of animals should at least be the subject of periodic review. This is an excellent bill and one that I think merits support.

[The statement follows:]

STATEMENT OF DR. NEAL D. BARNARD, PRESIDENT, PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE

Thank you, Chairman Bryan and members of the subcommittee, for this opportunity to testify in favor of S. 891, a most important act to modernize consumer product testing methods. I come before you as a physician and president of the Physicians Committee for Responsible Medicine, a national organization of more than 2000 medical doctors who promote preventive medicine and alternatives to animal research.

S. 891 will ban the infamous Lethal Dose 50 (LD 50) test, an archaic and cruel method of testing for product safety, and it will create a federal regulatory climate which is far more favorable to modern non-animal safety tests. In the opinion of the Physicians Committee for Responsible Medicine, this is essential.

Two types of tests are commonly performed in the pre-market assessments of new cosmetics and household products. In the first, known as the Draize irritancy test, substances which are often noxious are applied to the eyes and skin of live, unanesthetized rabbits and the resultant damage is observed. In the second test, known as the lethal dose, substances are fed to animals in increasing doses in order to determine the amount that kills a predetermined percentage of the test population. In the LD 50 test, that percentage is 50.

It is well-known that these tests are cruel to animals. But

what is not commonly appreciated is that these tests in no way protect the consumer from dangerous products. One needs only to go to any pharmacy or grocery store to view an array of readily available products which are toxic if swallowed, inhaled or splashed in the eye. Indeed, the National Injury Information Clearinghouse of the U.S. Consumer Product Safety Commission recorded, for 1988, 34,980 emergency room cases related to cosmetics and another 41,334 reportedly linked to household products.

Results from the LD 50 and the Draize tests are of no help in treating toxic exposures. Of these tests, Christopher Smith, M.D., a former clinical faculty member at the UCLA Emergency Medicine Center, said:

> "As a board-certified emergency room physician with over 17 years of experience in the treatment of accidental poisonings and toxic exposures, I have never used animal tests to manage accidental poisonings; to do so would be irrational." [Written testimony in support of H.R. 1635, submitted to the Subcommittee on Health and Environment, Committee on Energy and Commerce, U.S. House of Representatives, May 16, 1988]

Physicians rely instead on case reports, knowledge of the chemical makeup of the product, and experimental data from human clinical trials to determine the optimal course of treatment. Animal test results are simply not transferable to human experience.

Animal tests provide only the illusion of safety, because of the significant anatomical and physiological differences

between humans and animals. The LD 50 test, which this bill will ban, is an entirely unreliable predictor of a product's toxicity for humans. The LD 50 value of a compound depends on numerous factors, such as age, sex and strain of the animals, nutritional state, caging, room temperature, mode of application and concentration of the test substance, time of treatment, etc. An LD 50 value in one laboratory may differ considerably from one determined in another laboratory. Interspecies differences are particularly notable. These inadequacies led Dr. David Rall, then Director of the National Toxicology Program, to conclude in 1983 that:

> "The LD 50 test is now an anachronism. I do not think the LD 50 provides much useful information about the health hazards to humans from chemicals." [Rowan, A. Of Models, Mice and Men, 1984]

The Draize test is also highly unreliable. In 1948, when the test was four years old, researchers found that a concentrated solution of histamine phosphate caused only a slight and transient reaction in the rabbit eye. The test failed to predict the harsh reaction of even more dilute solutions in the human eye. This was one of the first failures of the Draize test, but it was not the last. Selenium sulfide, cresol, certain detergents, and a male hairdressing formula are among the substances that passed the Draize test, but were found to cause irritation and damage to human eyes.

The trouble with the Draize test lies in the significant differences between the rabbit's eye and the human eye. For

example, the pH level of human tears (7.1 to 7.3) is much lower than that of rabbits (8.2). A one-point difference in the pH scale means a ten-fold difference in the acidity of tears. The rabbit's cornea is about 30 percent thinner than the human cornea. Rabbits blink and tear at rates very different than humans. The "third eyelid" (nictitating membrane) which rabbits have, and humans do not, may change the animal's reaction to substances by clearing them away, or perhaps trapping them against the cornea.

Moreover, the Draize test is so subjective that different technicians can obtain vastly different results. Scientists at Carnegie-Mellon University distributed test substances to 24 different laboratories for Draize testing. They found much variability in results and concluded:

> " . .. it is suggested that the rabbit eye and skin procedures currently recommended by the federal agencies for use in delineation of irritancy of materials should not be recommended as standard procedures in any new regulations." [Toxicology and Applied Pharmacology, 1971]

There are many alternatives to outdated animal tests, and more are being developed every day. Indeed, many large cosmetics companies have already abandoned animal tests for more modern methods.

Avon, for example, has replaced the Draize test with the Eytex system, a non-animal alternative developed by the National Testing Corporation. The test utilizes a complex mixture of chemicals which simulate the structures of the human eye. Avon

has also established a computerized data base which contains historical testing data on Avon products and ingredients. Using this data base alone, the company approved 35 percent of its formulas in 1988.

The Noxell Corporation, makers of Noxzema, Cover Girl and other cosmetic products, recently accepted the agarose diffusion method as an alternative to the Draize test. This method, which involves testing substances on a thin layer of cells, has been used for 25 years to test the safety of synthetic materials in medical devices that come in contact with human tissues. It was adapted for testing cosmetic products and is included in the U.S. Pharmacopeia, an indication of official acceptance.

In fact, companies have an array of alternatives to choose from. Health Designs Inc. (HDI) markets a computer model for toxicity prediction which can predict, among other things, the rat oral LD 50, probability of mutagenicity, probability of carcinogenicity, and rabbit skin and eye irritation. And other methods, such as cell culture systems, the chorioallantoic membrane test and the tetrahymena method, have all demonstrated excellent capabilities for assessing the irritancy potential of new products.

Overall, these new methods are more efficient and cost-effective than the animal tests. For example, the agarose diffusion method, now used by the Noxell Corp., costs $50-$100 per product as compared to $500-$700 for the Draize test. And the

movement toward non-animal toxicity tests has created an exciting new industry. Arthur Benvenuto, CEO of Marrow-Tech, a cell and tissue culture firm, estimates a $1 billion market for alternative toxicity tests.

With all the advantages of alternative testing, it would seem that companies would be quick to embrace this modern technology. As we know, that has not been the case. The industry's reticence in adopting alternative testing methods is related to liability and regulatory, not scientific, concerns. That is why the second portion of this bill is so important.

In 1968, the case of Harris vs. Belton illustrated the use of animal testing for protection from legal liability. The plaintiff was a black woman who used a skin-lightening cream. Atra Skin Tone Cream promised a "lighter, lovelier skin beauty for you . . . a complexion fresh and bright as springtime." Unfortunately, the product caused the plaintiff's skin to be burned, scarred and darkened. She sued for damages. A small but significant number of other users of the product also had adverse reactions. The court ruled that the law does not prohibit the manufacture and sale of dangerous products, but simply provides that the customer be warned of potential adverse effects. The Atra product was labeled as potentially damaging for some users, and on that basis, the court ruled that the company was not responsible for damages to the plaintiff.

Thus some animal toxicity tests appear to be used primarily

for labeling and liability purposes. The federal government does not specifically require animal tests, and a great deal of confusion surrounds the issue of adequate tests for consumer safety and available alternatives to animal tests. According to Dr. Christopher Kelly, chairman of the National Testing Corporation, the barrier to change is deeply entrenched and the development of alternatives has been hampered by inconsistent product safety standards set by government regulators:

> "Current federal regulations limit the advancement of product testing techniques which are more technologically advanced than the older, less efficient methods." [Testimony in support of H.R. 1635, delivered to the Subcommittee on Health and Environment, Committee on Energy and Commerce, U.S. House of Representatives, May 16, 1988]

S. 891 will require federal regulatory agencies to review all regulations, guidelines and statements for product safety and to periodically review the status of available, non-animal toxicity tests. This is an essential and long-overdue move which will promote clarity, consistency and quality in product testing, while reducing an enormous amount of animal suffering.

You may hear, at some point during these hearings, that animal research is essential to medical progress. That highly-charged issue is not material to the debate here today. This legislation will not hinder research into cancer, heart disease, or birth defects. But it will make the consumer and the voter a bit more secure in the notion that their legislators are doi what they can to modernize testing methods.

A large segment of the American population does not support animal tests for the marketing of consumer products. A growing body of evidence suggests that there are compelling scientific reasons to advocate non-animal toxicity testing methods. It is time to bring consumer product testing into the modern age. As a physician and president of the Physicians Committee for Responsible Medicine, I urge you to vote in favor of S. 891.

Thank you to Senator Reid for sponsoring this most important bill, and to the members of this subcommittee for the opportunity to testify.

Senator BRYAN. Dr. Barnard, we thank you, and we will hear from you, Dr. Sevanian.

STATEMENT OF ALEX SEVANIAN, PH.D., ASSOCIATE PROFESSOR OF PHARMACOLOGY AND TOXICOLOGY, UNIVERSITY OF SOUTHERN CALIFORNIA, INSTITUTE OF TOXICOLOGY, ON BEHALF OF THE NATIONAL ASSOCIATION FOR BIOMEDICAL RESEARCH

Dr. SEVANIAN. Mr. Chairman, thank you very much for the opportunity to come and speak before this committee. I speak on behalf of the National Association for Biomedical Research concerning the Consumer Products Safe Testing Act. With the chairman's permission, a written statement is also being submitted for the record.

I wish to state for the record that the assertion that the use of lab animals in acute toxicity testing can now be eliminated—that is simply false. And I wish to emphasize that eliminating the LD50 test in its various forms—and I would like to emphasize at this point that the classical LD50 test is used in various forms now. It is very seldom simply a counting of dead animals. By limiting this LD50 test, we impose considerable impediment to the progress of valuable scientific methods for toxicity testing and we subject the public health to unwarranted risk.

Toxicity testing through the use of animals, specifically the LD50 test, and including the presently used approximate LD50 or limit test, represents the most reliable testing and confirmatory method available to date. It serves as a standard by which other non-animal test systems are verified and is presently instrumental in facilitating their development.

It is our hope to eventually replace the LD50 test with a panel of non-animal systems, but I do not see this as being accomplished in the foreseeable future.

In response to claims that the results from animal studies are dubious when applied to humans, I submit the following two points.

Number one, results from non-animal systems as they exist today are far more inconclusive and require much greater extrapolations to humans.

The other point is that countless toxicity studies with animals have already confirmed our subsequent experiences pertaining to the effects of these compounds on humans. The number of cases where animal results were non-predictive in terms of a chemical or drug are vastly outweighed by cases where they were very predictive. I cite as examples virtually all pharmaceuticals that have been marketed over the past decade.

Do not be misled by isolated examples where animal tests were by some parameters found to be inaccurate. No one asserts that the method is perfect. There are vast differences in responses of animals, but these can be compensated for by good systematic use of the LD50 test. Rather, consider the enormous number of drugs and chemicals whose margin of safety was accurately established through the use of laboratory animals.

An important contribution of animal models not adequately predicted by non-animal tests is the ability to identify possible problems not expressed as overt cytotoxicity, but problems that may require precautionary measures. The growing demand for chemotherapeutic drugs in today's market is a good example of that.

Now, we have heard about the various non-animal testing systems. The computer and structural analyses, the in vitro testing systems, and cell culture systems all represent good and developing non-animal testing systems. However, based on our current knowledge, these systems often require a verification using an animal model especially when positive results with a chemical or drug are obtained.

I submit that a combination of thoughtfully selected non-animal and animal tests represents the best battery of tests we have to ensure proper product testing and provide the optimum methods available to protect the public health. To arbitrarily remove a critical component of this battery cripples scientific progress and compromises public safety.

If we are to develop more accurate and reliable non-animal test systems, we must continue to employ the best gold standard we have available and that simply is an animal model testing system. LD50 at times is requested by regulatory agencies, as we have heard in a previous statement, often because the results of other non-animal tests are inconclusive and often the only remaining reliable method is to resort to an animal model.

It is important to consider the present state of science pertaining to non-animal testing systems, and you have heard what is referred to as the three R's, reduction, refinement and replacement. I would like to add a final R that the pharmaceutical industry often uses. Responsibility.

The process of reduction requires a reliable dose level to be set in vitro or in non-animal studies. Then we must know what the relevant toxic ranges are using a relevant animal model. Much of this information already exists from past LD50 data, and extrapolations to human effects have proven the reliability of much of this data.

For the future, the reduction process will require more LD50 studies. In most cases the limit test can be used to establish dose ranges of novel compounds. This will pave a sound scientific path for refinement of non-animal systems and perhaps the eventuality of replacing them. However, until this goal is achieved, we are faced with the responsibility of ensuring that products be accurately and thoroughly assessed for potential toxicity using the best means we have available.

The LD50 in its various forms has provided us with a large historical data base. Let's not ignore history and set it aside, but rather learn from it and utilize it to our best advantage.

[The statement follows:]

Statement of the

National Association for Biomedical Research

Mr. Chairman, I am Alexander Sevanian, Associate Professor at the University of Southern California School of Pharmacy's Institute of Toxicology. My doctoral training, research interests and graduate teaching responsibilities are in the fields of pharmacology and toxicology. I am a member of the Society of Toxicology and have also served as a consultant to industry. Today I am speaking on behalf of the National Association for Biomedical Research (NABR) whose institutional membership includes more than 325 universities, medical and veterinary schools, academic and professional societies, and also individual pharmaceutical companies, consumer product manufacturers and the major associations which represent these industries. NABR has encouraged its members to submit separate written testimony for the record. However, NABR wishes to offer a general statement on federal regulatory policy for toxicity testing. We very much appreciate your giving us the opportunity to do so.

Mr. Chairman, the Consumer Products Safe Testing Act is predicated on the unproven, and I submit false, claim that the use of laboratory animals in acute toxicity testing can now be eliminated in favor of nonanimal tests in most, if not all, cases. Let me say clearly that this assumption simply is <u>not</u> <u>true</u>. There are not scientifically valid, nonanimal methods available at this time to completely replace the use of animals in predicting toxicity. Federal agencies charged with protecting human and other animal health must continue to rely on the best means which science can provide to determine product safety. Currently, the best means may begin with valuable adjunct tests, but ultimately testing must progress to a whole, intact, living system, and

that is an animal model. As a toxicologist, I believe it would be a very dangerous federal policy to assume or to require, as this legislation does, that "nonanimal toxicity tests be used instead of animal toxicity tests." We are not ready, scientifically, for this.

A stated preference for nonanimal toxicity tests is ill-conceived federal policy not only at this time, but probably also for the foreseeable future. Congress' own Office of Technology Assessment has reported, after exhaustive study, that for most areas of scientific experimentation, including toxicity testing, total replacement of animal use is not likely, especially in the short term.

Perhaps the scientific community has itself contributed to the impression that proven, nonanimal alternatives already exist. As we have heard this morning, the use of animals in research and safety testing is a matter of public concern. In our eagerness to reassure the public that laboratory animals are used humanely, judiciously and only when necessary, scientists have emphasized the development of new tests and refinements which have reduced the number of animals necessary for toxicology studies and decreased or eliminated any pain in the animals that must be used. For example, the Ames Test is widely touted as a replacement for long-term animal studies. As you know, the Ames Test employs salmonella bacteria and rat liver cells to show whether a substance causes mutations. It is an extremely useful tool for evaluating a substance's potential to cause cancer. However, the Ames Test cannot be used in isolation because we are not certain that all carcinogens are in fact mutagens. It is still necessary to rely on

animal studies in some cases. Despite considerable progress in reducing the number of animals and refining our procedures, the science of toxicology is not in a position to do away with animal methods.

Also, I think the public may be confused by announcements that some companies do not test their products on laboratory animals or have stopped such testing. In these cases, product ingredients may have been tested previously in animals, and therefore do not require additional evaluation, or the safety of the products may be well-established based on a long history of human exposure to them. The fact that a given product does not require animal tests is not evidence that testing can be abandoned for all products. New chemicals, new uses of old chemicals and new mixtures of chemicals must be subjected to toxicity testing not only to satisfy federal safety requirements and state environmental or product liability statutes, but also so that unsafe products will not be marketed inadvertently. Not doing adequate testing violates both our moral and legal responsibility, and places people and animals at risk.

Attached to my statement is a white paper that includes a very basic description of the science of toxicology along with descriptions of why and how animals are used in toxicity testing, the types of tests, and the roles of federal regulatory agencies. The Foundation for Biomedical Research prepared this paper to help answer the public's questions concerning this rather complicated subject. I would like to request that it be included in the record, because I believe it is very useful.

Regarding some of the specific provisions of S. 891, Mr. Chairman, I offer the following:

First, I am very concerned about the underlying assumption of the Consumer Products Safe Testing Act that nonanimal tests not only exist, but are preferable to the tests we are now using to protest the public health and safety. Such nonanimal tests that now exist, and others certain to be developed in the future, must be proven in controlled and deliberate fashion to be predictive of the toxic potential of a substance. S. 891 makes the assumption that nonanimal tests are better and directs federal agencies to prove that they are not as predictive as current methods. This approach is the opposite of that which scientific procedure dictates and a foolhardy method for setting federal policy.

A second concern is that S. 891 would direct federal agencies not even to "consider" LD-50 test results for regulatory purposes. Federal laws require the consideration of all available toxicity data, and information cannot be suppressed. Where LD-50 values have been established based on prior testing, that information must not be ignored.

Let me discuss the LD-50 test a bit further. The LD-50 is the "classic" acute lethality test. As performed in the past, this test required up to 200 animals to obtain a high degree of precision. However, over the course of time, there has developed a general agreement within the field of toxicology that the precise calculation of LD-50 values is very

rarely, if ever, required in safety determination. Rather, a series of evaluations is preferred for testing a new substance. First, existing data on structurally related compounds can sometimes be used in lieu of animal testing to estimate relative toxicity. If not otherwise available in existing computer data bases, new data are obtained in approximate, or "limit," tests utilizing small groups of animals (3 to 6 animals are often sufficient). When no toxicity is observed, further testing is usually unnecessary, but ambiguous results mean toxic effects must be investigated further. In these cases clinical signs, symptoms and behavior are carefully monitored and tissues are examined to obtain the most complete information from study animals. This sequence is reflected in existing industry standards and practices and is consistent with federal regulatory requirements, including policies recently revised by the Food and Drug Administration and the Environmental Protection Agency.

In very rare cases, precise LD50 values may be required. The most often cited example of such a need is the determination of appropriate beginning human does of cytotoxic cancer drugs, but future needs could also arise.

In summary, <u>at least approximate</u> lethal dose information remains essential to prevent and treat accidental poisoning and other unintended acute exposures. A legislative requirement to rely only on nonanimal tests is premature at a minimum, based on our current state of knowledge and understanding of toxicity. Although the number of animals used for

acute lethality testing has been reduced dramatically, the need to use some laboratory animals for this purpose has not been eliminated.

On the subject of other acute toxicity tests, there also has been a great deal of progress in modifying procedures or reducing the numbers of animals needed. For example, in a relatively short period of time in scientific terms --- fewer than ten years -- the research community has developed dozens of in vitro tests we hope can ultimately replace the current Draize Eye Irritancy Test. Equally importantly, Draize test procedures have been refined for humane reasons.

Associations of consumer product companies have begun a validation process for the most promising candidate tests to replace the Draize test and have obtained commitments from federal regulatory agencies to discuss study results, which are expected very soon. I believe the details of these and other projects are being brought to the subcommittee's attention in written testimony for the record. Expert opinion suggests that a battery of tests may be the answer, and a combination of in vitro and in vivo techniques is a likely recommendation. In addition, in all probability replacement tests will be validated for particular product categories or chemical classes, not for universal application, as S. 891 would require.

The passage of laws or regulations determining the exact safety tests to be employed may only frustrate development of innovative tests. Acting prematurely to require new in vitro methods which have not been

adequately validated may result in their rejection and discourage further investigation.

Introduction of the Consumer Products Safe Testing Act has served to stir public interest, which is always healthy. These hearings have provided an opportunity to describe efforts by toxicologists and others to ensure the safety of products used by the American public. Continued success in our efforts will require the participation of many interested parties -- industry, government and the public. Science is responding as fast as it can. We trust the public will continue to closely monitor our progress. However, federal intervention is not necessary to encourage development of new methods, and legislation cannot take the place of necessary scientific evaluation.

Thank you for inviting NABR to appear before the subcommittee. I would be happy to try to answer any questions your may have.

Senator BRYAN. Dr. Sevanian, thank you very much.

I have been just glancing at this bill again. Now, let me ask you, Dr. Sevanian, do you read this bill as prohibiting the use of LD50 by congressional enactment?

Dr. SEVANIAN. What it does is it prevents its use in a testing procedure because the data cannot be submitted.

Senator BRYAN. The practical implication of that would be to make it of no value to use, would it not? If you couldn't use any data that is developed from it, would there be any purpose in using it then?

Dr. SEVANIAN. I am inclined to think that many companies—especially in the pharmaceutical industry—will continue to use the LD50 test in house in order to feel secure about the overall results.

Senator BRYAN. Could they do so if this bill is enacted?

Dr. SEVANIAN. I believe that they will nevertheless continue to do so.

Senator BRYAN. Dr. Barnard, Ms. Hazard or Dr. Stephens, what is your interpretation of this? The statute makes a finding that LD50 is an acute toxicity test on animals which has been shown to be inaccurate, misleading and unnecessary in product testing. It then goes on to say in another section, effective one year after the date of the enactment, Federal department or agency heads may not consider LD50 tests when determining product safety labeling or transportation. How do you read that, those of you who are advocates of the bill?

Ms. HAZARD. I believe the bill is intended to limit the government interpretation of those test results and has no impact or is not intented to direct what private corporations and industry would do to carry what they think is appropriate for testing the safety of their products. Obviously, from the testimony heard today, it is the feeling of individuals within government and the advocates of the bill, as well as the European community and the Japanese community that the LD-50 test is not necessary for product safety.

Senator BRYAN. Dr. Sevanian, do you agree? What would the effect be? In other words, if this should be enacted, if this should be prohibited, does that damage public health?

Dr. SEVANIAN. Well, first of all, there is an unrealistic time constraint here. We do not have alternative methods that industries can really hang their hat on and feel safe about.

Senator BRYAN. You are talking about alternatives to LD50.

Dr. SEVANIAN. Alternatives to the LD50 test.

Senator BRYAN. I understand that your testimony is much broader than LD50.

Dr. SEVANIAN. Yes, but setting all forms of the LD50 aside and simply relying on non-animal systems puts us in a very insecure position in terms of drawing conclusions on any given chemical and drug, particularly a new chemical or a new drug.

Too little is known about the variabilities of these non-animal testing systems. There is an enormous variability, particularly from the cell culture standpoint which is an area that I am actively involved in. The basis of my research is utilizing non-animal testing systems, and I know the limitations of cell culture methods. The kinds of extrapolations are enormous, and the pharmaceutical industry, for example, which utilizes these cell culture systems is very insecure about those results when viewed on their own.

Senator BRYAN. There is a distinction in some of the testimony which I do not see in the bill that you might be able at least to clarify for the record, any one of you. The term "classical LD50' has been used in some of the testimony, and paraphrasing some of the other witnesses, they have talked about modifications or variations. Now, that distinction does not seem to be made in the bill, or do I fail to pick that up?

Those of you who have the technical point of view, you might just make our record complete on that issue. That distinction appears to have been viewed as important by some of the testimony offered by witnesses, and yet I do not find a distinction in the bill between those two. Dr. Stephens, you look like you want to take a shot at that.

Dr. STEPHENS. Yes. I think for purposes of this hearing, the classical or traditional LD50 is the LD50.

There is some confusion now because the gentleman to my left is referring to the modifications of the LD50, such as the approximate lethal dose, the limit test, the up and down method, as forms of the LD50, and therefore he is apprehensive about the bill because he thinks that those other forms, which are not really forms of the LD50, would be prohibited. The bill does not prohibit the limit test, the approximate

lethal dose test and other acute toxicity tests. It would simply prohibit the LD50 test. So, I would reassure him on that point.

Senator BRYAN. Dr. Sevanian, does that give you any reassurance at all?

Dr. SEVANIAN. Not really.

Let's get a clear understanding of what the classical LD50 test is as it is applied today in a standard procedure. It is not simply a body count. You are dosing the animals. You are giving them various doses, and you have a good idea of a range of toxicities, not just the LD50. It is not simply increasing the dose and waiting for animals to die.

Furthermore, the animals are examined upon death. Pathology studies are done on these animals. They are utilized to the fullest extent. They are not just simply thrown away. So, a great deal of information is incorporated into the classical LD50 test as it is modified and applied today.

Senator BRYAN. So, your view is that the LD50 plays an important role, a necessary role, in terms of scientific investigation on issues that have long-term public health implications I presume.

Dr. SEVANIAN. Absolutely, and it is vital for the development of these alternative methods which we all want.

Senator BRYAN. Dr. Sevanian, do you agree with the overall intent of the legislation, that is to minimize the use of animal tests if there—and I underscore the word "if"—if there are alternatives that are equally efficacious?

Dr. SEVANIAN. Yes. Put in those terms, yes, absolutely.

Senator BRYAN. And if you do, what is wrong with requiring agencies of the Federal Government to, in effect, conduct a review and evaluation to see if, indeed, their procedures minimize the impact on animals? Is there anything wrong per se with that?

Dr. SEVANIAN. Only in terms of the standard operating procedures that are employed by industries and various laboratories to decide whether or not a specific test is done, if there is a scientific basis for doing so or a long, drawn-out bureaucratic one.

Senator BRYAN. To the proponents of the bill, one of the criticisms that we hear a great deal of these days is that in the United States, compared to western Europe, the length of time it takes for a new drug which is in the testing pipeline to ultimately reach the market is far longer, years and years and years, and the criticism is made that the expense is enormous. There are, further, those that would argue that the delay is unnecessary in terms of public health, and there are those who would even go so far as to say that Americans are being deprived of medications available in western Europe and other communities which have a strong scientific community.

Now, I would presume that going through a process in which you have to evaluate the efficacy of each procedure to determine that there is, in fact, no non-animal alternative—wouldn't that further delay and exacerbate that process?

Dr. BARNARD. In my view it would certainly not.

Senator BRYAN. Would you develop your rationale for the answer please, Dr. Barnard?

Dr. BARNARD. Certainly. First of all, there is a finite number of tests that are required by any Federal agency, and it may well be that if there has been no progress in any given area, that the process of stating that the alternatives are simply not good enough to replace the animal test, that process would be a rather rapid one.

On the other hand, when there is significant progress, its recognition by Federal agencies would only speed the process of drug approval.

However, I think it would be naive to assume that the very slow and cautious process by which drugs are approved in this country would be affected one way or another by the passage of this bill.

Senator BRYAN. I have had some experience in the bureaucratic process, although not from a technical and scientific point of view. Don't you think that a requirement to promulgate regulations which specify that non-animal toxicity tests be used instead of animal toxicity tests unless the Federal department or agency head determines that in certain limited case the non-animal toxicity test has less validity than the animal toxicity test—don't you think that is going to take at least some time?

Knowing that even those who are great advocates of government would never argue that speed is one of its attributes, it just seems to me that from a strictly mechanical point of view that really imposes some burdens in the sense of time. Those of you who are proponents may believe that whatever delay is occasioned would be justified in light of the achievement that would be accomplished. But you don't think there would be any delay?

Dr. BARNARD. No doubt there would be some time required. I do not know if that would be a long or short time by each Federal agency.

However, there is a benefit in terms of time, the timeliness of the testing procedure itself. The agarose diffusion method that I mentioned earlier is an excellent example. A typical Draize test takes at least three days to finish, and if there is any signs of irritation in the eye of the rabbit, the test does not finish for three weeks. Often it has to be repeated because of various problems, for example, if not enough animals have reacted one way or the other in order to give a definitive result.

When Federal agencies decide that alternative methods such as the agarose method that Noxell is now using are adequate and encourage their use, testing will be much faster.The agarose method just takes a matter of a couple of days. It does not require a three week process.

So, it certainly will be an investment of time by Federal agencies. But every time an alternative is validated and incorporated into the testing armamentarium we obviously have a much speedier testing battery.

Senator BRYAN. Ms. Hazard and Dr. Stephens, would you care to amplify on Dr. Barnard's comments?

Ms. HAZARD. Thank you, Mr. Chairman. I just have one comment, and I know it has been a concern with other Senators with whom I have spoken with on this issue.

This bill is not intended to create requirements that the agencies must follow with reference to each new drug or new product that comes on the market. It is not a requirement that would have to be fulfilled with each submission by an industry. It is not intended that the government would look and see whether there was an animal test done for a particular product and whether there is a non-animal alternative available. This bill merely directs the government to look at those regulations that are already have on the books in the Federal Register and to make sure that those general requirements for product classes, not for individual products, are as technologically advanced as they can be and, hopefully, non-animal.

I think that certainly in the short run when the regulations are undergoing a review, as any review, it will take some time and some commitment on the part of the agencies. But once that review is complete, the bill should in fact expedite the ability of—those individuals in industry, those corporations in industry that want to switch to non-animal tests.

The corporations that have made the decision to switch in the past year. Avon, Revlon, Colgate-Palmolive, have had to engage in a series of meetings with the FDA to bring in their experts to explain to the regulators what their tests are and to get some commitment from the agency that these alternative tests would at least be acceptable to the government. That would not be a procedure that corporations would need to go through if the government had a blanket approach to approving alternatives.

Senator BRYAN. Dr. Stephens?

Dr. STEPHENS. I would just add a couple of things, one, that the agencies already claim to be monitoring progress in this area. So, presumably their formal review would not be overly burdensome.

And secondly, that there currently is an atmosphere of indecision and uncertainty among companies that want to make progress in this area, and part of the problem is with the agencies. So, we can get beyond this problem and we can let the companies get back to doing what they do best, producing consumer products by passing this bill.

Senator BRYAN. Dr. Sevanian, you indicated in response to an earlier question that, in terms of minimizing the use of animals in research, if there are equally efficacious non-animal testing procedures that you agree in general with that philosophy. I do not want to misstate your position, but that is what I thought I understood you to say.

And if I did, let me follow that up with a question that was prompted by the comment that Mr. Kimm made. Mr. Kimm said, that a decade ago, if this kind of discussion were held within the scientific community, there would be greater resistance than there is today, again to paraphrase.

My question to you is if that general attitude or philosophy that you have shared with us today is a prevailing view, what procedures are presently being implemented within the scientific community to make some judgments independent of what statute or regulation may require to minimize the use of animals in testing if there are, indeed, other procedures available that are equally effective.

Dr. SEVANIAN. This is an active program in both industry and academia. Many, many laboratories, many independent and corporate investigators are specifically assigned the task of examining alternative methods.

The point that I stressed in my testimony was that they still utilize animals as a gold standard because of the enormous historical data base. And after all, we are looking at the effects on an entire intact organism, not of substances in a test tube.

What is viewed now by the pharmaceutical industry is what I would call a numbers game. An enormous number of animals will now have to be utilized to verify a lot of proposed alternative testing systems. And let me use a specific example, the Eytex and the Draize.

A company with which I consult, a large pharmaceutical firm, has a division that is utilizing the Draize test. They are also aware of the Eyetex system. But now they are faced with 36 compounds that they have already characterized, that they have to go back and make comparisons between the Eyetex and the Draize test to feel satisfied that the correlations are in fact good. This will take time. It will also utilize more animals now so that others can be spared later. So, we are playing with a numbers game.

And I hope to see some day that the Draize test will be replaced by a non-animal alternative, but I see the problems and the length of time and the numbers game that is involved in achieving that goal.

Senator BRYAN. Dr. Sevanian, I thank you.

If any of the other witnesses who would like to make a brief statement about anything that may not have been covered in the colloquy that we have just had, let me tender the floor to you for one last comment, if you have any such comments to make.

Dr. BARNARD. I would simply want to say that the process of development of alternatives—we are always in gray areas. Different companies disagree. And as the other witness stated, it may be that some animals will even be used in the validation process.

This bill does not restrict that process or impede it. If anything, it facilitates that very process that we all recognize is necessary.

Senator BRYAN. Any other comments or questions?

Well, in that case, we thank the panel for their informative and very helpful testimony. The record, obviously, will include their comments.

And I would ask this panel, as I did the previous panel, to make yourself available to respond to any questions that members of the subcommittee who could not join us this morning might have and would be submitting to you in writing. And we will hold the committee record open for a period of time to do just that.

This subcommittee hearing is adjourned, and the subcommittee stands in recess.

[Whereupon, at 10:35 a.m., the subcommittee was adjourned]

ADDITIONAL ARTICLES, LETTERS, AND STATEMENTS

STATEMENT OF DR. CHRISTOPHER KELLY, CHAIRMAN, ROPAK LABORATORIES

Thank you Mr. Chairman and members of this Committee for the opportunity to testify in support of S891, the Consumer Products Safe Testing Act. My name is Dr. Christopher Kelly, Chairman of the Board of National Testing Corporation. I hold a doctorate degree in Pharmaceutical Sciences from the University of Southern California, and I am the inventor of the first non-animal pregnancy detection test, BETA-CG .

In 1972, I founded and was Chairman of the Board of American Diagnostics Corporation. After twelve years of designing and producing medical diagnostic test kits, I sold American Diagnostics, with its pregnancy kits and drug monitoring products to Hoffman La Roche. As a condition of the sale, I agreed to remain out of the field of medical diagnostics for 10 years. I turned to the development of in vitro toxicity tests to apply the expertise and experience I had acquired in medical diagnostics. In my professional opinion, a great deal of exotic and esoteric research had been done, yet none of the proposed methods would lead to the advanced alternatives to animal testing that industry and government were seeking.

In 1985, I founded National Testing Corporation to explore the field of in vitro toxicity testing and to research and develop more accurate alternatives to the current methods for measuring the irritancy of chemical materials.

We have developed and hold the patent on the EYTEX System which is an in vitro test for determining acute ocular irritancy. EYTEX is a substitute for the Draize Rabbit Eye test for most applications and would eliminate the animal suffering associated

with the Draize procedure. I have attached a copy of our patent as Appendix A.

Responsible manufactures of household products, and cosmetics have long recognized the need to test their ingredients and formulations for ocular safety.

The growing concern for consumer protection, occupational hazards, household safety, and product liability increases the importance of evaluating chemical ingredients in products and labeling them accordingly. Also, new federal regulations require chemical manufacturers in the United States to provide toxicity data, including ocular toxicity, for each hazardous chemical produced or imported. These factors coincide with public pressure to reduce or eliminate animal testing and to substitute *in vitro* methods whenever possible. The EYTEX System addresses these needs by providing a chemical method which allows rapid evaluation of ocular safety for a wide variety of chemicals and mixtures.

In the past, ocular irritancy has been evaluated *in vivo*, using animal subjects. The most common procedures are based on the rabbit eye irritancy test described by Draize in 1944 (1). Although this approach has been used to evaluate the ocular irritancy of a wide variety of chemicals, it has several major drawbacks: the subjective nature of measurements (2,3,4,5), the variability of results obtained in different laboratories (6,7,8), the length of time required for testing, the high cost of performing each test, and the poor correlation with data on ocular irritancy in humans exposed accidentally to small

quantities of ocular irritants (9,10,11,12). These scientific limitations together with growing public interest in the elimination of unnecessary animal experimentation emphasizes the need for in vitro methods to assess ocular irritancy (13). These in vitro alternatives should correlate with the existing literature on animal data and the individual databases around the world.

The EYTEX procedure is rapid, accurate, objective, reproducible, and relatively inexpensive, and therefore is a practical alternative to in vivo methods. Extensive studies have shown an excellent correlation of ocular safety measured by the EYTEX method with results obtained using the Draize method (14,15). The EYTEX System is particularly appropriate in several specific applications, such as the screening of new ingredients for drugs, household and cosmetic products, the monitoring of production batches to assure product safety, and the testing for product stability. I have attached more detailed information on the EYTEX System as Appendix B.

In the spring and summer of 1987, a large multi-lab study was conducted by twelve industrial, university, military, and independent laboratories to test the accuracy of the EYTEX System. One hundred and thirty unknown samples were run by the EYTEX method and the results were compared to the Draize rabbit eye test, demonstrating an over all correlation of 96% (16).

The use of the EYTEX System in six governmental, university and industrial laboratories to perform standardized measurements of chemical irritation was presented at Johns Hopkins University Symposium on Progress in Alternatives to Animal Testing (17).

This inter-laboratory study established an overall correlation of 90% between laboratories. These results demonstrated that the EYTEX System is a standardized, transferable in vitro method.

Several other independent studies, joint studies, and double blind studies have been conducted during late 1987 and early 1988 to enlarge the database to over 500 compounds. The Laboratory Services Division of National Testing Corporation is testing samples at a rate that will expand the database to over 1000 chemicals and formulations by the end of 1988.

Despite the successful correlation of the results of this test with the Draize method, and its advantages over Draize in terms of cost, reproducibility, simplicity and time, the market growth of the system has been hampered by inadequate and inconsistent standards set by government regulators to determine product safety. Current federal regulations limit the advancement of product testing techniques which are more technologically advanced than the older, less efficient methods.

The barrier to change is deeply entrenched. The regulations obstruct any technological advancement by defining the standards for product safety in terms of the physiological reactions produced in an animal to a specific substance. With references to ocular safety, the Consumer Product Safety Commission for example, defines an "eye irritant" in terms of the physical manifestation of the response of a rabbit when the substance is dropped in the rabbit's eye (21). To comply with these regulations, a manufacturer must either determine that a product is highly toxic based on "human experience" or conduct tests with animals (22).

The CPSC has confused the issue of what may be required to comply with regulations by stipulating in their Policy Statement that "neither the FHSA (Federal Hazardous Substances Act) nor the CPSC regulations require any firm to perform animal tests" (23).

S891 will require agencies which have the responsibility for ensuring the safety of products to review the myriad of regulations, statements and guidelines issued in this area and then to create clear and equitable performance standards for innovative and improved test methods, such as the EYTEX System. This will promote consistency and quality in product testing while at the same time reducing the number of animals used and eliminating nearly all the animal suffering associated with ocular safety testing. I urge the committee to support S891 and to vote this Bill favorably out of the Sub-committee and full Committee.

THE JOHNS HOPKINS UNIVERSITY

CENTER FOR ALTERNATIVES TO ANIMAL TESTING

November 6, 1989

Senator Richard Bryan
Chairman Consumer Subcommittee
U.S. Senate
227 Hart Office Building
Washington, D.C. 20510

Dear Senator Bryan:

Thank you for your request to the Johns Hopkins Center for Alternatives to Animal Testing (CAAT) for information regarding alternatives to the use of animals in product safety testing to be included in the record of the Subcommittee hearing on November 8, 1989.

The CAAT was established by a grant from the Cosmetic, Toiletry, and Fragrance Association (CTFA), with additional support from Abbott Laboratories, Amoco Foundation, Inc., Avon Products, Inc., Bristol-Myers Company, Charles River Laboratories, The Geraldine R. Dodge Foundation, Estee Lauder Companies, Exxon Corporation, IBM, Johnson & Johnson, Mary Kay Cosmetics, and the National Institutes of Health to develop a research program focusing on alternative approaches to evaluate product safety by using in vitro or other non-whole animal testing procedures, which will substantially reduce the number of animals used in testing.

We at the CAAT believe that animal use in routine product testing should be eliminated as soon as possible, and we are working hard to achieve that goal. Accurate non-animal methods will spare animal lives, provide better information about safety, and save companies and consumers money normally spent on expensive animal tests.

We cannot recommend, however, that industry cease animal testing immediately. Until non-animal tests are proven at least as effective as animal tests - and they have not yet been - companies must continue to use animal tests to fulfill their moral and legal obligations to insure the safety of their products. In the meantime, we are aware that most companies are beginning to use new procedures that reduce the numbers of animals used and relieve possible discomfort felt by the animals that are used.

Animal research helps physicians, veterinarians, and scientists find new ways to prevent and treat disease and injury in both animals and humans. Therefore, it is important to distinguish between routine product testing which eventually may require no animal use, and research which will continue to require animal use for the foreseeable future.

I have enclosed a recent issue of the CAAT newsletter to give you a better

School of Hygiene and Public Health
Department of Environmental Health Sciences

615 N. Wolfe St., Baltimore, MD. 21205-2179
301-955-3343

Senator Richard Bryan
November 6, 1989

understanding of the work we do. Also enclosed for the record is a reprint of an article published in the August, 1989 issue of the Scientific American along with other materials which will be of interest. Your name has been included on our mailing list so that you will receive the newsletter free of charge.

Sincerely,

Alan M. Goldberg, Ph.D.
Associate Dean for Research

AMG/jsp

Enclosures

Toxicology Letters, 35 (1987) vii-xi
Elsevier

Guest Editorial

ALAN M. GOLDBERG

Center for Alternatives to Animal Testing,
The Johns Hopkins School of Hygiene and Public Health, Baltimore, MD (U.S.A.)

INTRODUCTION

The need to assess the safety of commercial and consumer products has been highlighted during the last several years. Technology and advances in chemistry have provided us with the opportunities of new products, of new formulations and of new entities. It is widely accepted that in excess of 100 000 chemical compounds are currently in the market place for which we have little, if any, data on which to assign risk. Additionally, the methods that have been accepted for the assessment of toxicity, tests like the LD_{50} and eye testing in the rabbit are methods that were introduced about half a century ago. These tests, although generally not required by regulation, have become standard because of history and tradition.

The increased awareness of potential hazards to chemicals has led to demands by consumers for more testing, for more effective testing and for less expensive testing. This demand for increased testing has been countered by many in the animal protection movement for the decreased use of animals in testing strategies. The requests from the animal protection movement among others confused the issues of basic biomedical research with routine product safety testing.

Coincidental with social awareness and the need for product safety are major developments from the scientific standpoint in terms of providing new methods and new approaches using a new biology to address these very real problems. Cell, organ and tissue culture methodologies, which were developmental in basic biomedical research 15 or 20 years ago, were not even utilized in toxicological research 10 years ago and were not considered for use in routine safety evaluation.

ALTERNATIVES

The term alternative is a relatively recent addition to the campaign literature of the animal protection movement, and there is still widespread disagreement over its precise definition. Some organizations use the term to refer only to techniques that replace completely the use of animals in a particular area, for example, a computer model to predict LD_{50} values. However, others follow the definition developed by Russell and Burch in 1959; they defined an alternative as any technique that replaces the use of animals, that reduces the need for animals in a particular test, or that

refines a technique in order to reduce the amount of suffering endured by the animal. Thus, use of the up-down method to determine an acute toxicity value is an alternative to the classical LD_{50} test because fewer animals are required. Today these three Rs, Replacement, Refinement and Reduction, represent the common definition of alternatives.

The alternatives most commonly considered are cell, tissue and organ culture, computer modeling, and the use of minimally invasive procedures and endpoints that produce less stress. Although more and more toxicological research is being conducted in vitro, the potential of culture methods in toxicological protocols and hazard assessment is only now beginning to be utilized and evaluated. This is the result of public pressure, the availability of new developments in basic biology, and increased recognition among scientists of the opportunities in vitro methods provide for risk assessment.

ADVANTAGES AND DISADVANTAGES TO IN VITRO METHODOLOGY

The use of culture methods must be developed and implemented cautiously in toxicology testing and hazard assessment. Obviously, a single culture cannot mimic the complex interactions of all cell types in the body, no matter how exquisite the experimental design. In vivo metabolism may be simulated to some extent, but not completely, and integrating functions such as immune reactions and phagocytosis are developmental at this time. In addition, culture systems are relatively static and the dose of the test chemical reaching the target system and the duration of contact may not be the same as those that occur in the in vivo test. Culture methodology also presents physical problems regarding the solubility, stability, and biophysical effects of the test compound.

On the other hand, culture techniques have great potential once investigators have acquired the background knowledge to ask highly focused and specific questions. The static nature of culture methods is also an advantage in that the dose and duration of contact of a test chemical can be precisely determined, and far less of the test chemical is required for in vitro investigations than in in vivo tests. Therefore, one can easily set up replicate cultures and generate more data in a shorter time.

One of the most exciting aspects of culture methodology in toxicology is that one can use human tissue. Such studies have been limited in the past because of the difficulty of growing and maintaining differentiated human cell types in culture. But technical problems are being steadily overcome. Important developments in the last years include improvements in the quality control of media and the plasticware provided by manufacturers, improved quality control in the laboratory, better media formulations for the growth of normal cells as well as for cells exhibiting specialized functions (e.g., heart cell contractility and melanin production by melanocytes), and improvements in cell separation and cloning techniques.

APPROACHES TO DEVELOPING IN VITRO METHODOLOGY

The empirical approach to the development of methodology is problematic. The questions asked are generally not focused and correlations develop prior to fundamental understandings. Additionally, the results tend to be somewhat unpredictable. Should this be the case in the development of in vitro toxicological methods, we will unfortunately have provided supplementary testing strategies but not replacement testing strategies. This will leave us with the dilemma of attempting to use the in vitro methodologies without being able to rely on them.

Model development utilizes systems that try to mimic in vivo systems. Generally, the model system is neither complete nor faithful in all aspects of the system being modeled, but it tends to provide useful information if the data are not overinterpreted. In those model systems where a single aspect of an integrated response is examined and the data are interpreted in that single system, this technique can provide meaningful inferences for the evaluation of chemical effects.

The mechanistic approach to the development of in vitro methodologies should be based on a thorough knowledge of the metabolism, kinetics, and biology of the system or species to be examined; e.g., if the metabolic pathways are understood, or if it is known that the parent compound produces the toxicological insult, then one can develop a system to examine the mechanisms by which the chemical(s) produces its effect. One can then evaluate the adverse chemical or physical effects that lead to a significant functional loss in the tissue or system. This approach allows the in vitro system to be derived from the species under study, and it also provides a better understanding of chemical–biological interaction and the consequences of that interaction. Using this approach, it will be possible to develop appropriate, interpretable, simple and reliable in vitro methodologies for toxicity testing.

From a scientific viewpoint, the mechanistic approach is not only preferable but necessary. In vitro methods will be more acceptable and will develop rapidly when the knowledge base has advanced far enough to permit a focus on mechanisms. However, this is a goal yet to be achieved and in the interim, we have to use whole animal approaches and to continue to develop other measures which will rely on tissue culture techniques, and other in vitro methodologies that provide quick, reproducible accurate methods for the assessment of safety.

UTILIZATION OF IN VITRO METHODOLOGY

If one traces the utilization of tissue culture in toxicity assessment, one can see remarkable progress having already been made in just the first few years. The first early approaches to the use of in vitro tests looked at exclusion of dye as an attempt to measure viability and integrity of the cell membrane. A second level which provided some greater degree of sensitivity looked at leakage of endogenous constituents of the cell into the medium, for example, enzymes. Most recently there has

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been interest in more functional aspects of the cell with the first attempts looking at the levels of specific components such as proteins, to the next level of advancement by studying the rate of protein synthesis, and most recently to the identification of alterations of specific proteins. These changes in approach, which seem small when described in a few sentences, required quantum leaps in our thinking and equally great advances in the methodology available to us.

At this stage of the development of these more sophisticated systems, it is necessary to carefully evaluate the reproducibility, transferability and interpretability of the methods in product safety assessment. Significantly, correlative studies alone will not provide this information. A coordinated and highly structured approach to validating many methods against each other, against our current methodology, and against the data available on human experience, will provide us with usable in vitro tests. This will provide an approach to the utilization of in vitro methodology in product safety evaluation and risk assessment.

However, to eliminate animal testing at this time would constitute an abrogation of the toxicologist's responsibility to insure safety and will pose a risk to human health that government, industry and the public will find unacceptable.

VALIDATION

Validation is defined here as the process by which new in vitro test systems are developed to the point where they can provide data for toxicological risk assessment of chemicals. A classical example of the process is illustrated by the historical development of the Ames assay for evaluating the carcinogenic potential of chemicals. This test has taken over 15 years to reach the stage where it has been fully integrated into the carcinogenicity testing strategy. By defining the process, it can be more effectively carried out. The major steps in the process include: (1) standardization and transfer of technology, (2) identification of a 'gold' standard for evaluation, (3) understanding the importance of a mechanistic basis, (4) defining the chemical classes to be evaluated by the test battery and (5) providing a historical precedence and initiation of a data base.

Using a highly coordinated effort, the final step in getting in vitro methods accepted for risk assessment, validation, can be effectively accomplished.

CONCLUSIONS

As with any new innovation, it clearly takes time to educate the audience for which the innovation will be used. Alternative or in vitro methods in toxicology are innovations. The use of animals in toxicity testing is and will continue to be a major source of data in assigning risk and establishing regulatory requirements. However, it is abundantly clear that in vitro methodology will also become a major part of our armamentarium for the establishment of safety.

The use of animals provided us with a first way to quantify and assess risks. The limitations to this approach, although incredibly successful in protecting the public from risk, have also been in some cases less than satisfactory. We are all familiar with the anecdotes and the published literature showing the value of animal testing and its limitations.

With the beginnings of in vitro methods being used in risk assessment of commercial or industrial products, a new understanding of the process of validation is apparent. The questions that are being raised now, which pose a problem for in vitro toxicology, are also the same ones that will provide us with the opportunity for more effective risk assessment methodology. When one is attempting to evaluate a methodology, a first question that must be raised is against what is the methodology being validated. For example, if one is attempting to use tissue culture methodology to replace eye irritancy testing strategies, does one validate against the rabbit test or does one validate against data obtained in humans? Clearly, there is a more substantial data set for the Draize rabbit eye irritancy test than there is for human accidental exposure. However, the species that one is attempting to protect by doing the testing is the human.

When developing in vitro testing strategies, how does one identify and handle the different kinds of chemicals and formulations. If one is testing for water soluble products, one set of battery or tests may be needed while different batteries may be needed if testing for aqueous insoluble material, mixtures, solids, powders or dusts. Do we set up our test batteries on physical or chemical properties or on endpoint measures?

The development of in vitro testing strategies in toxicology provides us the unique opportunity to reexamine from both an academic, as well as commercial and regulatory viewpoints, how to better provide data for risk assessment. If one was attempting to validate an animal test at this point in time, such as the Draize eye irritancy test, would it meet the criteria that we're establishing for the new in vitro tests?

In vitro methodology will not in any single step replace animal testing. There will be several phases by which in vitro testing will be done along with the standard in vivo procedures. As the in vitro tests become more refined and more defined, then they will begin to play a greater role in the evaluation of toxicity. Once we develop the data base, the history, and the confidence in appropriately developed in vitro tests, we should then expect to see that in vitro testing will become our primary approach to safety evaluation with final confirmation of expected lack of toxicity in appropriate animal species.

STATEMENT OF THE AMERICAN SOCIETY FOR THE PREVENTION OF CRUELTY TO ANIMALS

The American Society for the Prevention of Cruelty to Animals (ASPCA), appreciates Chairman Bryan's leadership in holding these hearings on S. 891. We are pleased to submit written testimony for the record in support of the Consumer Products Safe Testing Act.

The ASPCA, America's first humane society, represents some 375,000 members nationwide and directly cares for more animals each year than any other humane society in the country. The ASPCA promotes the humane care and treatment of all animals through its humane education and legislative programs.

It has been a year and a half since hearings on a House companion bill were held. Since then many changes have occurred which make today's hearing timely and helpful.

Timeliness of Hearings

In the written comments, a number of large cosmetic companies have implemented non-animal tests by substituting alternatives for the classical LD50 and Draize tests.

Last month the European Commission decided to stop supporting use of the classical LD50 test and to urge members to replace it with existing and more humane alternative tests.

Commendably a small but significant number of corporations have taken bold steps to find and begin using appropriate alternatives to animal acute toxicity testing. Unfortunately, other manufacturers are reluctant to move forward and employ alternatives which yield both better scientific results and less suffering to animals because of the long-standing and ubiquitous

uncertainty in government and regulatory policy on the use of animals in acute toxicity testing.

It is our hope that these hearings and subsequent support by this committee for S. 891 will put an end to this confusion.

The LD50 Test

Acute toxicity testing measures the adverse effects of a chemical substance in laboratory animals after an intense, brief exposure. Toxicologists help assess the risks to the public in using drugs, pesticides, food preservatives, and industrial chemicals which contain these test substances. Acute toxicity testing can provide a broad range of information on the toxic effects produced by a single dose of a test substance. Until recently, the LD50 test using up to 200 animals was the most commonly used method for assessing acute toxicity.

LD50 stands for Lethal Dose 50 Per Cent or Median Lethal Dose. This is the amount of a substance, given in a single dose, that will kill half of a test group of animals within a fairly short specified time period, usually two weeks.

The test was developed by a British scientist, J.W. Trevan, in the 1920s as a quality control for a few dangerous drugs. Initially, the test was used to assess the exact strength of different batches of these drugs to determine the fine line between what dose would cure and what dose would kill patients.

Eventually, the use of this test moved beyond standardization and was incorporated into the routine toxicological protocols of other classes of chemical compounds.

Modern Science

Starting in the late 1960s, however, the scientific literature began to articulate the limitations of the LD50 as a measure of acute toxicity. It became increasingly apparent during that decade that toxicologists had been practicing bad science. What had once been a test designed for the standardization of highly potent impure drugs was being used indiscriminately for thousands of chemical substances. The limitations of the test were delineated by numerous scientists.

These experts argued that althouqh the LD50 had assumed special importance over the years, and the numerical values had come to be accepted as an index of toxicity, the test yielded very limited information. In fact, they insisted that the precise knowledge of LD50 values is of little practical use.

In addition, toxicologists such as Morrison, Quinton, and Reinert, have been pointing out since approximately 1967 that the LD50 test is scientifically questionable. In fact, numerous scientists including Zbinden, Morrison, Baker, and Tattersall, have established the variability of LD50 values by pointing out the many factors which can influence the test procedures. Zbinden and Flury-Roversi in 1981 enumerated the long list of factors that can influence the LD50 test and cause widely-varying results. These

factors include the age, weight, sex, genetic make-up and health of animals, and the diet, ambient temperature, housing conditions, and feeding routine given to the animals. As Zbinden explains, some of these sources of variability could be controlled through a standardization of test procedures, but because scientists can scarcely be expected to arrive at one optimal protocol or the LD50 test procedure for all purposes, it is impossible to claim this test has universal and constant validity.

Other scientists have highlighted the fallibility of considering the LD50 test results as absolutes by examining the reproducibility of test results obtained in different laboratories. Two different studies have shown highly disparate values obtained from tests conducted in different laboratories and even within the same laboratory testing the same substance.

Finally, critics of LD50 argue that the precise LD50 figure cannot be used to indicate accurately the possible lethal dose in human beings. The transferability of data results from animals to humans is suspect. In 1982 Zbinden stated, "clinical experience shows that the LD50 value determined in animals rarely bears a meaningful relation with the lethal dose in man." This question of transferability of data is related to the differences of susceptibililty between species. For instance, penicillin is highly toxic in guinea pigs but usually nontoxic in humans.

Barriers to Change

There are three predominate factors at work in slowing the move away from the LD50 tests.

1. Regulatory Confusion. Many toxicologists have stated that the strongest reason why the classical LD50 test is continued by researchers and industry is the lack of clear regulatory direction from the administrative agencies. The regulations, guidelines, and protocols of many federal agencies either directly or indirectly mandate LD50 testing by manufacturers, industry, and researchers. When Baker wrote in 1969, that "in spite of the limited value of these [the LD50] tests, they were insisted upon by various regulatory authorities," he identified a long-standing problem.

2. Fear of Litigation. Another reason for the perpetuation of the test has been industry fear of product liability suits. With the increasing litigiousness of consumers and the escalating damage awards and costs to industry for unsafe products, manufacturers and their scientists feared that even useless tests had better be conducted to protect themselves against the failure to meet their duty of care. Furthermore, until a broad base of scientific literature was established, industry needed to assure itself protection by observing the state-of-the-art; in other words, conducting the pervasive and popular LD50 test.

Today, however, we are in limbo. As shown, the scientific community readily agreed that the LD50 testing is not

a thorough indicator of poisonousness and, thus, the state-of-the-art defense arguably could be achieved by not conducting the LD50 test. But because federal agency policies and regulations remain ambiguous and misconstrued, too many manufacturers and captains of industry remain unwilling to blaze new paths without clear, federally-approved protocols to follow.

3. Scientific Recognition of Alternatives. Although there are a number of alternatives scientifically equal to or better than animal tests, and economically more advantageous, the old pattern and practices have prevailed in many instances. So long as federal agencies continue to accept LD50 results, the use of alternatives is undermined.

Why The American Society for the Prevention of Cruelty to Animals Supports S. 891

This bill is a positive, simple piece of legislation. It will reduce animal pain and suffering yet is not punitive. It does not require expensive and labor-intensive enforcement. It requires neither an appropriation of tax monies nor the creation of a new bureaucracy.

The Consumer Products Safe Testing Act does two things: first, it stops the consideration of LD50 test data results by federal agencies when determining product safety, labeling, or transportation requirements; second, it requires federal agencies to review and evaluate their endorsement or use of animal toxicity tests and then to put forward regulations which specify the use of

non-animal toxicity tests in place of animal toxicity tests when non-animal alternatives are available. The effect of these measures will be two-fold. The federal government will raise the standard for toxicity testing by no longer tolerating or being complicitous in perpetuating the use of an outdated scientific procedure. And the bill will foster the advancement of other methods of toxicity testing which do not harm animals.

Both of these results are highly desirable. The federal government best serves the interests of science, industry, and the general public when it promotes current, sound, and efficient methodology. Similarly, when the federal government requires scientists and researchers to use non-animal toxicity test methods when appropriate, the search for valid, humane, alternative advancements will be hastened and people and animals alike will benefit.

Recommendations

The ASPCA would like to urge this committee to consider, for its report, the following suggestions to be implemented with the passage of the bill.

First, confusion seems to remain within the scientific community as to the true nature of the federal regulatory requirements for the LD50 test data. Although many agencies have stated they no longer require the LD50 test, many companies and scientists believe they must run the tests and submit the data if applications are to be considered thorough and complete. All

agencies should do an internal check to see what policies, guidelines, statements, protocols, or directives cause this double message. Such documents and policies must be changed. In addition, affirmative action should be taken by the agencies. A clear position paper or announcement should be sent to all major toxicological testing laboratories, toxicological societies, chemical trade associations, and others in private industry interested in acute toxicity testing results stating which tests the agency will accept.

Second, current data submissions are often poorly logged and recorded. For instance, we have been informed that at the Food and Drug Administration data are submitted in such a manner that the LD50 results are not logged separately from other test results. The agency has no way of isolating such data submitters from others in order to inform them that such data are not required or needed by the agency. Similarly, much duplicated data are frequently submitted to each agency. Thousands of studies are performed each year, but the toxicological data are not stored in a retrievable manner and as a result scientists cannot review and evaluate such results quickly. Duplication, time, and money are lost and the test animals are caused unnecessary pain, suffering, or death.

Finally, in order to promote non-animal alternatives to testing the agencies themselves should also develop, research, validate, and implement appropriate alternatives. When agencies

can ask industry to do what they themselves are trying to do, alternatives will seem an achievable goal, not merely a dream for the future.

The Consumer Products Safe Testing Act will advance the health, welfare, and safety of the public while reducing animal suffering and death. We strongly support this measure and urge the Senate to enact it into law.

STATEMENT OF THE AMERICAN HEART ASSOCIATION

The American Heart Association (AHA) submits the following comments on S. 891, the Consumer Products Safe Testing Act. AHA, one of the world's largest voluntary health agencies in the United States, is the only such group that dedicates all of its human and financial resources to the reduction of disability and death from cardiovascular diseases and stroke. Despite progress in this area, cardiovascular diseases remain the leading cause of death in the United States.

As a result of research, prevention and education programs, striking advances have been made in the fight against cardiovascular diseases and stroke. The AHA has always placed its major emphasis on preventing disease, and has consequently invested heavily in scientific research. Since 1949, the AHA has invested more than $754 million in research to combat diseases of the heart and blood vessels. Over 30 percent of AHA's yearly revenues are used to support promising scientific investigations. Hundreds of lifesaving medical innovations are directly and indirectly due to the AHA's sponsorship of research into life-threatening cardiovascular diseases.

Millions of Americans today are healthy, and other millions are alive, because of advances in the prevention and treatment of cardiovascular diseases. Age-adjusted death rates from heart attack, stroke and related diseases are declining. From 1976 to 1986 the age-adjusted death rate from coronary heart disease has declined by 27.9 percent and that from stroke has fallen by 40.2 percent. The decline is largely related to changes in life style and development of methods of treatment, many of which are based upon animal experimentation. These events encourage medical scientists to believe that most heart attacks, strokes, and hypertension can ultimately be prevented or their onset can be deferred so that they do not cripple or kill people prematurely.

Effective prevention and treatment of disease depends on accurate knowledge about the causes of disease, on information about how disease affects the body,

on drugs that combat disease on devices that work, and on operations that cure. The knowledge, material, and skills on which prevention and treatment are based have come from a wide variety of sources--basic scientific disciplines such as chemistry, biology, physics, engineering, mathematics, and many others including, observation of naturally occurring disease in human and animal populations, and experimentation on human subjects and animals.

Great benefits have resulted from applications of this knowledge, including the heart-lung machine, repair of congenital heart defects, heart valve replacement, cardiopulmonary resuscitation and the use of drugs to combat hypertension and prevent stroke. Continued progress in the prevention and treatment of cardiovascular diseases depend on maintaining access to all these sources of knowledge.

Animal experimentation has been challenged as unjustified on both scientific and ethical grounds. Currently, no completely satisfactory method exists to model the extraordinary complexity of the human cardiovascular system, which nourishes and interacts with every organ in the body. Generation of new knowledge, testing of new drugs, and the refinement of new devices and operations that affect the cardiovascular system, therefore, require animal experimentation.

Ethically, the main choice is between improvements to human and animal health through animal research versus restrictions on animal research use that cancel our hope for life-saving progress. Confronted with such a choice, we have usually decided that experiments on animals should precede the extending of experiments to human beings.

The American Heart Association, dedicated to improving human welfare by fighting cardiovascular diseases and stroke, invests funds contributed by the American public in basic research on heart diseases. That research, of necessity, involves the use of animals

AHA a founding member of the American Association for Accreditation of Laboratory Animal Care (AAALAC), has been in the forefront of strongly endorsing responsible and humane use of animals in biomedical research. We believe that this approach is essential and necessary to biomedical research and education in the prevention, reduction and treatment of diseases of the heart and blood vessels. No AHA research funds are awarded for the support of investigations or projects without proper documentation of compliance with appropriate animal care and use standards. These standards are regularly revised to reflect current understanding and practices. Most recently, they have been modified to bring our awards application and granting procedures into complete alignment with the Public Health Service (PHS) standards. AHA's action in awarding grants is governed by our statement entitled "Assurance of Responsible Use of Animals."

In accomplishing our mission, we work in active partnership with related federal research, education and prevention programs. These consist of activities of the Public Health Service (PHS), including the Centers for Disease Control, Food and Drug Administration, the National Institutes of Health, and the Office of Disease Prevention and Health Promotion. We strongly endorse and support the Department of Health and Human Services (HHS) comments on S. 891 presented to your Subcommittee on November 8, 1989 by Assistant Secretary for Health, James O. Mason, M.D.

The Consumer Products Safe Testing Act would prohibit federal agencies from accepting LD50 test results and would require a published justification for requiring or recommending any animal toxicity test in light of non-animal alternatives. AHA concurs with HHS's detailed analysis that the enactment of this legislation would impede biomedical research and drug development by restricting the choice of scientific methods and by requiring burdensome justification for scientifically essential animal use. To ensure continued advancements in biomedical research scientists must enjoy freedom of choice in selecting research methods

Frequently a combination of methods are used. We reiterate our above statement that continued progress in the prevention of cardiovascular diseases depends on maintaining access to all sources of knowledge. Also, the justification requirement would create an administrative burden and would delay research.

Moreover, we support the contention that this legislation is based on the erroneous assumption that there are currently available valid non-animal models for acute toxicity tests. Mr. Chairman, although progress has been made in this area, unfortunately, this is not yet the case. As we mentioned above, presently, there is no completely satisfactory method to model the extraordinary complexity of the human cardiovascular system.

The American Heart Association appreciates this opportunity to comment on S. 891 the Consumer Products Safe Testing Act. We firmly endorse HHS's assessment that enactment of this legislation would have devastating repercussions for the Nation's health. Thank you for your careful consideration of our concerns reflected in the endorsement of HHS's comments.

STATEMENT OF FORMER LABORATORY TECHNICIAN

LESLIE FAIN

As a former employee of the Gillette company and on behalf of Friends of Animals 120,000 members I would like to submit the following statement in support of S. 891, the Consumer Products Safe Testing Act. I worked at the Gillette Company's animal testing lab in Rockville, Maryland for over 1 1/2 years as an animal care taker, animal care technician I and animal care technician II. I am certified by the American Association for Laboratory Animal Science as a Laboratory Animal Technician.

Gillette performed both lethal dose toxicity and Draize irritancy tests. I frequently observed these types of tests being performed. From what I observed, I have no doubt that the tests caused the animals involved tremendous pain and suffering.

ORAL TOXICITY

The lethal dose testing at Gillette included oral, dermal, and inhalation toxicity studies. The LD50 (lethal dose 50%) is an oral toxicity test. An example of the oral lethal dose toxicity test performed at Gillette was the force feeding of shampoo to rats in a test designed to purposely kill 100% of the animals. Even though the results were known before hand, in order to determine the LD50 value, 100% of the animals were poisoned to death with the shampoo being tested. On many occasions I saw technicians force feeding substances to rats. When I would check on the rats later in the day many would be bleeding from the nose, mouth or anus. Some would be unconscious. Some would be dead. Many had bloated stomachs and many appeared to be in a great deal of pain. At Gillette killing

100% of the animals was required for probit analysis, a method used to determine the LD50 value.

DERMAL TOXICITY

The rabbits used in the dermal toxicity tests (also known as percutaneous LD50) had approximately 75% of their fur shaved off, had their skin abraded with a hypodermic needle and then had the test substance applied to their skin. They were then wrapped in gauze and plastic and stuffed into a restraining box (they could not move or turn around while in the box) for at least 24 hours without access to food or water. On numerous occasions I heard rabbits squealing in pain and terror and upon further investigation I would find a technician stuffing a panicked rabbit into a restraining box. When the rabbits were removed they were subjected to a shower of water and tossed back into their cage. Many of the poisoned rabbits would die a lingering death that often took several days. Many had blistered, burned and peeling skin. No form of anesthetic was ever administered to the rabbits and they were never humanely killed to put them out of their misery even though it was very apparent that they would die anyway (the rabbit would be moribund and would not have eaten or drank for many days). Many of the dermal toxicity tests resulted in the death of up to 100% of the test animals.

INHALATION TOXICITY

Another acute toxicity test is the LC50, lethal

concentration 50%. An acute inhalation toxicity test. In this test animals, usually rats or monkeys, are placed in an air tight chamber. On several occasions which I observed the technicians took turns manually spraying hairspray in four minute shifts for an hour into a chamber of rats. They used a total of 15 cans of hairspray. The study director told me that for me to get the same effect I would have to seal myself into my bathroom and spray hairspray for an hour. This test method was so sloppy and archaic that the rats in the corners of the chamber often died from alcohol poisoning because the hairspray condensed above them and dripped on them during the hour long test. The rats that survived were observed for wheezing, bloody discharge, lethargy and death. After 14 days any remaining survivors were killed and dissected. As with all laboratories there were never any survivors -- all animals were eventually killed.

DRAIZE EYE IRRITANCY

I saw rabbits with bloody discharges oozing from their eyes in Draize eye irritancy tests. The rabbits had been given a drop of anesthetic before the test began but according to Gillette employee Robert Noland, in a memo dated January 8, 1985, "the anesthetic administered before the test initiation did little to mitigate the suffering of these animals." No other anesthetic was administered to the rabbits. They were forced to linger in agony with the test substance eating away at their eyes. In the same memo Mr. Noland describes the rabbits as

having endured "unnecessary pain and suffering." As in all Draize eye irritancy tests nothing was done to treat the injured eye.

I saw hundreds of rabbit's eyes blinded and burned with substances ranging from shampoo to ink (in some cases the products had already been on the market for many years). The rabbits involved were forced to endure considerable pain and suffering while undergoing the Draize eye irritancy test. Many rabbits who were used in the eye test were recycled into the Draize skin irritancy test.

DRAIZE SKIN IRRITANCY

I observed rabbits being prepared for, subjected to, and killed at the end of many Draize skin irritancy tests. The rabbits were shaved (approximately 50% of their fur was removed) and a test substance was applied to their abraded skin (the abrasions were made with a hypodermic needle). The rabbits were then wrapped in gauze and plastic and a large plastic collar was fastened around their neck. At this point the rabbits would be carried by the ears and tail and thrown back into their cages where they would "go wild" and thrash about (often hitting the top and sides of the cage) trying to remove the collar (this is documented by Gillette employee Robert Noland - in a memo dated January 8, 1985). On many occasions I found rabbits with their paws caught in the collar laying on their backs suffocating or unable to move. Once the tests were completed the rabbits would

either be killed or recycled again for another test.

On several occasions rabbits died from eating the gauze and plastic bandages. The plastic gauze lodged in their intestines and blocked the flow of feces, causing death.

These were just a few examples of the pain and agony I observed while employed at Gillette. The Draize and lethal dose acute toxicity tests on animals are crude and unscientific. They cause terrible suffering to millions of animals each year. They do not protect human health and safety.

I urge you to support S. 891 which will prohibit the use of results from the classical LD50 test by Federal agencies when determining product safety, labeling or transportation requirements for the purpose of Federal regulation. In addition, S. 891 will require the periodic review of animal toxicity testing regulations. This is necessary to encourage the use of more humane and more accurate test procedures than those currently used. The tests described above were developed in the 1920's - 1940's. They are outdated. Many more accurate and humane alternatives have been developed. But, unfortunately, companies are hesitant to utilize them without encouragement and direction from regulatory agencies. S. 891 will direct those agencies to replace the animal tests with <u>validated</u> alternatives as they become available.

STATEMENT OF ADELE DOUGLASS, ON BEHALF OF THE AMERICAN HUMANE ASSN.

Over the past ten years, there has been a major change in public attitudes on the use of animals in toxicity tests, particularly for tests on such consumer products as cosmetics and household products. Congress has responded to this public concern by directing various federal agencies to increase their efforts to fund and implement alternatives. However, these agencies have been slow to take appropriate and decisive action. By contrast, a number of companies have started providing funds for a variety of programs that seek to develop adequate alternative tests that do not use animals and a number of corporations now have active and aggressive programs focused on alternatives.

In view of the foot dragging by federal agencies, the American Humane Association contends that Senator Reid's bill, the Consumer Products Safe Testing Act, is needed to focus regulatory attention on the alternative non-animal tests and to promote the development of appropriate initiatives to address public concerns about animal suffering in safety tests (without any sacrifice of public safety).

In particular, the Consumer Products Safe Testing Act would eliminate the use of the classic LD50 test on

animals. This test was first developed in 1927 for the purpose of standardizing therapeutic agents that could not be characterized by chemical means. The LD50, obtained by forcefeeding 60 to 200 animals with the chemical until approximately half die (the Lethal Dose 50%), came to be viewed as a standard part of the toxicity profile for a new chemical. However, the test uses far too many animals simply to generate a statistically precise measure. This precision is totally unwarranted since the LD50 of a particular chemical may vary by a factor of 100 to 1,000 from one species to another and rodent LD50's do not correlate well with human lethal doses. In any event, the measure that is of most concern on human toxicology is not the dose that will cause death, but the dose that will cause serious illness.

Over the past ten years, toxicological opinion of the classical LD50 has shifted dramatically. Toxicologists used to regard the measure as a cornerstone of toxicology. Today, most toxicologists now argue that the classic LD50 as unnecessary and unhelpful. Dr. Gerhard Zbinden, an internationally respected toxicologist, has said that the classic LD50 is obsolete and that "Clinical experience shows that the LD50

value determined in animals rarely bears a meaningful relation with the lethal dose in man." Dr. David Rall, the Director of the National Toxicology Program, has called the classic LD50 an anachronism.

Most toxicologists now argue that the classic LD50 test be abolished and that acute toxicity be determined by using only 6 to 10 animals to gain a rough quantitative estimate of toxicity together with more information on the qualitative toxicity of the chemical. Recently (9/22/88), the Environmental Protection Agency has issued a new policy statement on acute toxicity that specifically urges industry not to submit classic LD50 data but to determine acute toxicity using only a few animals. The FDA is also encouraging companies not to rely on the classic LD50.

Although animals are still required to determine the acute toxicity of chemicals, the Consumer Products Safe Testing Act does not address this issue but only abolishes the use of the classic LD50 for certain specific purposes. Even more important, the bill puts the regulatory agencies on notice that the Congress expects them <u>actively</u> to seek out and promote the development of toxicity tests that use fewer (or no)

animals and that reduce animal distress. While the public expects consumer and other products to be safe, it is also calling for more humane approaches to safety evaluation. The pursuit of alternatives offers the best hope not only for the reduction of animal use and suffering but also for improving the speed and effectiveness of toxicity testing.

We urge the Congress to pass this bill to send a strong message to the public that outdated and anachronistic tests are not to be tolerated because of bureaucratic inertia and to direct regulatory agencies that are an integral part of their mission.

FASEB FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY

9650 ROCKVILLE PIKE • BETHESDA, MARYLAND 20814

TELEPHONE 301-530-7000 · CABLE ADDRESS: FASEB, WASHINGTON, D.C.

Corporate Members
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Executive Director

JOHN R. RICE, C.P.A.
Comptroller

November 21, 1989

The Honorable Richard H. Bryan
Chairman
Subcommittee on Consumer
Committee on Commerce, Science
and Transportation
SH-227 Hart Senate Office Building
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

The Federation of American Societies for Experimental Biology (FASEB), which is composed of seven scientific societies representing almost 30,000 biomedical researchers, wishes to record its opposition to enactment of S. 891, "The Consumer Products Safe Testing Act." The underlying assumptions of the bill have no basis in scientific fact and its enactment would not achieve the benefits claimed.

As President of FASEB and having just completed a term as President of the American Society for Pharmacology and Experimental Therapeutics, I am well acquainted with the views of leading scientists most familiar with the issues surrounding toxicology testing. The view of the overwhelming majority of those scientists is that while we have a responsibility to continue to develop non-animal alternatives to the LD-50 tests, alternatives do not exist that can entirely replace testing with animals. Alternatives have, however, enabled scientists to supplement and reduce the number of animal tests required. But, to mandate the replacement of all animal testing would be to jeopardize the integrity of research on which the public health and well-being depend.

Clearly the accuracy and predictive value of any non-animal alternatives must be established through laboratory experience. My colleagues will continue to explore such alternatives, but in doing so the efficacy of these alternatives must always be evaluated against the baseline data accumulated through animal testing. In other words, animal tests will be necessary to establish the value of alternatives.

In this brief letter I have not detailed the scientific basis for these strongly held views. Should you or your staff require such detail I would be happy to assist or direct you to one of our members more directly involved in the relevant technology.

I appreciate the thoughtful approach you have taken on this emotional issue. I hope you will continue to enlist the best available scientific advice as you seek the greatest benefit to the public welfare.

Sincerely,

William L. Dewey

William L. Dewey, PhD
President

November 6, 1989

The Honorable Richard H. Bryan
Chairman, Consumer Sub-committee
#227 Hart Senate Office Building
Washington, DC 20510

Dear Senator Bryan:

We understand that a hearing will be held in the Consumer Sub-committee on S. 891, the "Consumer Products Safe Testing Act" on November 8, 1989. Tom's of Maine encourages the cessation of the classical LD-50 tst and a review of alternatives to animal toxicity testing.

Tom's of Maine manufactures a line of natural personal care products including toothpaste, deodorant, anti-perspirant and shampoo. Our products are distributed nationally through health food stores and food and drug stores in select markets throughout the country including, (in the D.C. area) Giant, Safeway, People's Drug and Fantle's.

The Food and Drug Administration, the sole federal agency with regulatory jurisdiction over the safety of our products, does not require us to conduct any animal tests on our ingredients or finished products. We do believe, however, that other firms may be conducting animal tests which are unnecessary and ineffective for assessing human safety solely to comply with government regulations. As a firm committed to consumer safety as well as humane testing, we find this unconscionable.

The Federal Government should be a leader in assessing and promoting the development and use of new technologies in this area. We encourage the U.S. Congress to promote this policy and for this Committee to favorably consider S. 891.

Please contact me should you require any further information.

Sincerely,

William G. Stuart
Product Manager

WGS/njm

1927J/1

Railroad Avenue P.O. Box 710 Kennebunk, Maine 04043 USA Telephone (207) 985-2944 Telex 950047

CONSUMER PRODUCT SAFETY COMMMISSION

STAFF COMMENTS ON S.891

FOR THE CONSUMER SUBCOMMITTEE, SENATE COMMITTEE
ON COMMERCE, SCIENCE AND TRANSPORTATION

The Commission staff has reviewed Senate Bill 891, which encourages the development and use of product testing procedures which accurately reflect human reactions to products but which do not rely upon animal models. These objectives are desirable, and the Commission shares the concern about the unnecessary use of animals in testing of products to determine their toxicity or other hazardous effects. However, we are also concerned about the bill's presumption that suitable non-animal alternative tests exist. This is not so for the basic toxicity tests that are sometimes necessary to determine the hazards posed by consumer products. We are additionally concerned that Section 3(a), as currently written, would prohibit the consideration of existing LD_{50} test results and could adversely affect consumer safety by prohibiting the use of much, if not most, of the existing knowledge about the toxicity of consumer products.

The Commission administers the Federal Hazardous Substances Act (FHSA), 15 U.S.C. Sections 1261-1277, which requires cautionary labeling of products that present a potential hazard to the public. Neither the FHSA nor the implementing regulations require product testing on animals to determine the hazards posed by the product. The hazard can be determined on the basis of prior human experience, existing animal test data, or expert opinion. In those instances when these other sources of information are inadequate and animal testing is necessary, the FHSA describes "highly toxic" in terms of animal test results (15 U.S.C. Section 1261), and the implementing regulations prescribe how such tests shall be performed (16 C.F.R. Section 1500.40-.42). The Consumer Product Safety Commission has also published an animal testing policy (enclosed) which minimizes the use of animals, minimizes the pain and suffering during such tests, and encourages the use of available alternatives to obtain the necessary safety data. The major provisions of this policy are:

a) Use of human experience, existing animal test data on products with similar chemical composition and/or physical properties, or expert opinion in lieu of animal tests.

b) Use of the limit test for LD_{50} determinations. This was chosen since we only need to know that a product has a toxicity of greater than 5 grams per kilogram or less than 50 milligrams per kilogram, not an exact number. Thus, we have reduced the number of animals per test from 60 to 80 to 10 to 20.

c) Elimination of testing of products which are skin irritants for eye irritancy. Past experience has shown that, if a product is a skin irritant, it is also very likely to be an eye irritant.

d) Use of pH as an indicator of eye irritation. Products that have a pH of less than 2 or greater than 11.5 are presumed to be eye irritants.

e) Use of ophthalmic anaesthetics when eye testing is required.

f) Elimination of the use of stocks for holding animals when skin irritation test is required. The animals are free in the cage and have access to feed and water, thus reducing stress and dehydration.

This bill prohibits the use of LD_{50} test results and severely restricts the use of other acute toxicity tests, including those based on reduction and refinement of animal tests used in the determination of product safety, labeling, or transportation requirements. The CPSC staff has examined the use of animals in acute toxicity tests and the availability of non-animal tests to replace animal toxicity tests and concluded that:

a) Animal toxicity tests have been successful for the most part in protecting and promoting the health and safety of humans.

b) Non-animal toxicity tests are not sufficiently developed and/or validated so that they can replace the animal tests. The development and validation, including the establishment of reliability and reproducibility, along with relevance and interpretability of the data generated, is a long and costly process. It may take several years or more before non-animal alternatives are sufficiently validated to replace even some animal toxicity tests. Therefore, animal toxicity tests are at present necessary.

c) Meanwhile, animal alternative tests, based on the principles of reduction and refinement, should be developed and used to reduce the number of toxicity tests, to reduce the number of animals per test, and to reduce the animal suffering during such tests.

d) Classical LD_{50} tests should not be conducted unless scientifically justified and approved by an Institutional Animal Care and Use Committee. Instead, other tests, such as the limit test, approximate lethal dose test, etc. should be used.

The recommendations of the Interagency Research Animal Committee (enclosed) are consistent with these conclusions.

International Organizations, such as the Organization for Economic Cooperative Development, U.S. and foreign technical organizations, such as the Society of Toxicology, the British Toxicology Society, and industrial organizations, such as the Soap and Detergent Association, the Cosmetics, Toiletries and Fragrance Association, and the Pharmaceutical Manufacturers Association have also examined this issue and have come to the same conclusions as indicated above.

The collective work by U.S. and foreign government agencies, industry, scientific organizations, and scientists on the alternative tests, using reduction and refinement of existing animal tests, has resulted in a reduction in the use of animals of 64% for household products and a reduction of 87% in the use of animals for Draize eye irritation tests. The testing of corrosive and severely toxic products, which in the past resulted in suffering of animals during the tests, has been nearly eliminated.

The current Animal Welfare regulations promulgated by USDA and the Public Health Service animal care and use policy severely restrict the use of animals for procedures that cause suffering without justified scientific necessity and which are approved by an Institutional Animal Care and Use Committee. The CPSC staff and other federal agencies endorse these policies and will continue to encourage the development and validation of suitable non-animal alternatives.

The CPSC staff believes that the prohibition on the use of LD_{50} test results is inappropriate and restrictions on other animal toxicity tests required by S.891 are premature since non-animal alternatives have not been validated to replace the animal tests. The bill as currently written would prohibit the agencies from considering previously generated LD_{50} data in the determination of product safety, labeling, or transportation requirements. Since the LD_{50} test has been so heavily relied upon for many years as part of the toxicity evaluation of both chemicals and consumer products, the prohibition of considering it would eliminate most reference sources for use in considering the safety of products. This would have the effect of allowing products on the market pending the development of human experience, thereby allowing the adults and children of the United States to become the test subjects. The staff suggests that the bill should at least be changed to prohibit the consideration of only those LD_{50} tests conducted after the passage of the law.

In conclusion, the staff believes that the passage of this bill would seriously jeopardize the protection currently afforded the users of consumer products and introduces a substantial and unnecessary paperwork requirement for federal agencies. Further, the staff believes that this bill may be unnecessary in light of the recommendation of the Interagency Research Animal Committee on LD_{50} testing (enclosed) and the activities of the federal establishment towards the use of animal and non-animal alternatives in safety testing and research.

Enclosures

INTERAGENCY RESEARCH ANIMAL COMMITTEE (IRAC)

RECOMMENDATION ON LD_{50} TESTING

RECOMMENDATION

The LD_{50} tests evaluate lethality from exposure to a substance or product and are used to A) classify them for safe transportation and labeling, B) provide information for treatment of acute intoxications, C) standardize certain biological products, D) set dose levels for subsequent toxicity studies, and E) provide data for evaluation and validation of alternative test methods. The LD_{50} tests have become controversial among toxicologists, animal welfare organizations, legislators and the public primarily due to the ethics of using a large number of animals and evaluating only the mortality. IRAC explored this issue and recommends the following:

1. The **Classical** LD_{50} test should not be conducted unless specifically justified for reasons of scientific necessity and approved by the Institutional Animal Care and Use Committee.

2. Toxicity testing procedures based on the principles of **reduction** and **refinement** (e.g., Limit Test, etc.) should be used until alternative test methods are validated.

BACKGROUND

IRAC has reviewed the recommendations relevant to the LD_{50}, of the Federal Agencies and the international organizations involved in acute toxicity testing. These organizations include the Environmental Protection Agency, the Food and Drug Administration, the Consumer Product Safety Commission, the Department of Transportation, the National Toxicology Program, the Organization for Economic Cooperation and Development, the British Toxicology Society, and European Chemical Industry Ecology and Toxicology Center. There is consistency aming the policies on the following points:

1. The use of the **Classical** LD_{50}, which is an evaluation of the number of deaths per dose level and requires the use of many animals to establish the desired statistical confidence limits, is unnecessary for the determination of acute toxicity.

2. Tests involving animals are currently essential in the determination of acute toxicity, which is a step in the assessment of the potential hazard of a chemical or product.

3. There are recommended alternatives to the **Classical** LD_{50} test utilizing the principles of **reduction** and **refinement** (see attached - Summary of Current Policies).

4. A validated **in-vitro** test or battery of tests is presently not available that can be used as a replacement for tests on animals in the determination of the LD_{50} dose. There are tests in various stages of development and/or validation. Rather than wait for one universally validated tests(s), the process of development and/or validation may be accelerated using a group of related chemicals or products. For that group, validated test(s) could be accepted as a screen or as a replacement of LD_{50} tests on animals.

DEFINITIONS

1. **Classical LD_{50}**

   Median Lethal Dose, LD_{50}, is a statistically derived dose with specified confidence limits, and is expected to cause mortality in 50% of the treated animals within a given period. In the determination of this dose, death is the only end point. Each test involves 60 or more animals, needed to arrive at a desired confidence level, and concurrent administration of the test substance to animals in 5 or more exposure groups of both sexes.

2. Limit Test

   In this test, a single dose that determines regulatory categories for substances or products is used on 5 to 10 animals.

SUMMARY OF CURRENT POLICIES

U.S. ORGANIZATIONS

A. Consumer Product Safety Commission:

o Strongly discourages **Classical LD_{50}**.
o Recommends other alternatives - existing animal data, prior human experience, expert opinion.
o Recommends the Limit test.

B. Department of Transportation:

o Discourages the use of the **Classical LD_{50}**.
o Recommends the use of existing animal data and human experience.
o Recommends the Limit test (48 hours).

C. Environmental Protection Agency:

o Discourages the use of the **Classical LD_{50}**.
o Uses Structurally Related Activities (SAR) to obviate the need for testing on animals.
o Recommends the Limit test: in the absence of lethality at 5 g/kg dose, no further test is needed.

o When testing beyond the limit test is conducted, recommends use of abbreviated test methods such as the approximate lethal dose, the moving average, and the up-and-down methods. Stresses the need for multiple end point evaluations, including onset, nature, reversibility of effects and gross necropsy.

D. Food and Drug Administration:

o Does not require the use of the **Classical LD_{50}**.
o Accepts alternatives.
o Refers to the Limit test.

E. National Toxicology Program:

o Does not use **Classical LD_{50}**.
o Uses in-depth toxicology with many end points.

INTERNATIONAL ORGANIZATIONS

A. Organization for Economic Cooperation and Development:

- o Discourages the use of Classical LD_{50}.
- o Recommends the Limit test (2 g/kg dose).
- o When compound related mortality occurs in the limit test, then 5 animals per dose, at least 3 dose levels are used to produce a range of toxic effects and mortality rates; clinical observations and pathological investigations conducted.

B. British Toxicology Society:

- o The LD_{50} should only be determined with any accuracy where scientifically and ethically justified. Such cases are relatively rare.
- o Examination of few animals in detail rather than many for statistical purposes.
- o Limit tests could be used, provided animals in distress are killed humanely, if this would not interfere with the objectives.
- o For classification of substances and preparations, a fixed-dose procedure targeted to acute signs could replace the current practice of LD_{50} determination.

C. European Chemical Industry Ecology and Toxicology Center:

- o Acute toxicity profiles are important.
- o Classical LD_{50} test is seldom necessary.
- o Protocols exist for estimating lethal dose.
- o LD_{50} above 2 g/kg is irrelevant.
- o Regulations should not specify minimum number animals.
- o Procedures for the selection of a toxicity class should be encouraged.
- o Acute toxicity data may be unnecessary for the protection of human health from some products.
- o Predictions based on alternatives as an aid to dose selection should be encouraged.

Attachment - Bibliography